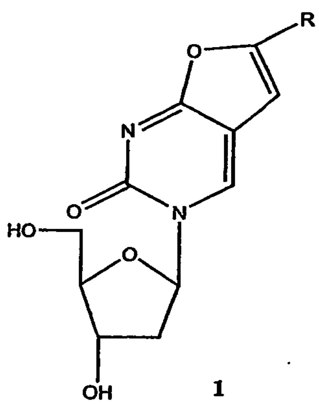
HETEROCYCLIC COMPOUNDS FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

The present invention relates to a chemical compound and to its therapeutic use in the prophylaxis and treatment of viral infection for example human herpes viruses, particularly and human cytomegalovirus (HCMV). Cytomegalovirus is the aetiological agent in CMV retinitis and other viral infections, which can cause considerable human illness and suffering.

It has previously been noted that nucleoside analogues of the structural types 1 and 2 exhibit a potent and selective antiviral effect (McGuigan *et al* J. Med. Chem. 1999, 42, 4479-84 and J. Med. Chem. 2000, 43, 4993-97):



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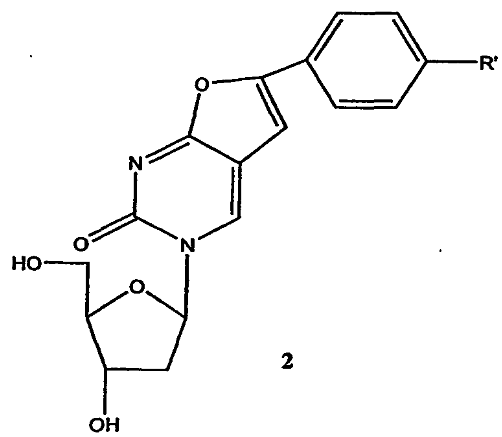

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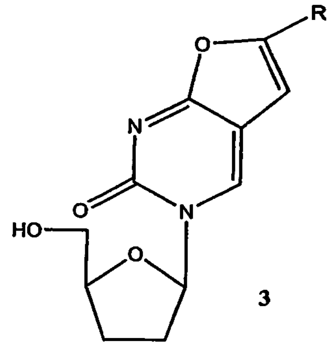
Optimal structures are 1, R=C8-C10 and 2, R=pC_5Ph. Further details are given in WO 98/49177 and WO 01/83501, respectively. The compounds exclusively inhibit Varicella zoster virus (VZV) in a VZV – thymidine-kinase dependent fashion, functioning in a classical nucleoside analogue manner, of obligate intracellular nucleoside kinase-mediated activation (Balzarini *et al*, Mol. Pharmacol. 61, 249-254, 2002).

It has recently been noted that dideoxynucleoside analogues of 1 have a pronounced but quite distinct activity against another member of the herpes family, namely human cytomegalovirus HCMV. The optimal structure of these agents was identified as 3 and is described in WO 01/85749.



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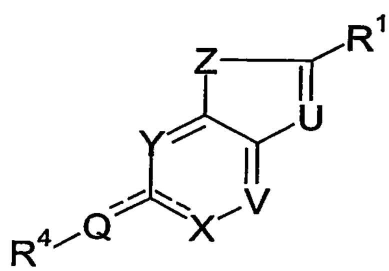
These agents would have been expected to act via a classical nucleoside mechanism, requiring 5'-phosphorylation before they would exhibit antiviral activity. As such a 5'-OH and a quasi-nucleoside structure with a sugar or close analogue was deemed necessary.

It is an object of the present invention to provide novel compounds, in particular novel compounds not requiring phosphorylation for, for example, biological activity.

It is a further object of the present invention to provide novel compounds for therapeutic use in the prophylaxis and treatment of viral infection, for example, by cytomegalovirus.

According to the present invention there is provided a chemical compound having the formula (I):



wherein:

R^1 and R^4 are independently selected from alkyl, aryl, alkenyl and alkynyl;

Z is selected from O, NH, S, Se, NR^5 and $(CH_2)_n$ where n is 1 to 10, and CT_2 where T may be the same or different and is selected from hydrogen, alkyl and halogens, and R^5 is alkyl, alkenyl or aryl;

Y is selected from N, CH and CR^6 where R^6 is alkyl, alkenyl, alkynyl or aryl;

Q is selected from O, S, NH, N-alkyl, CH_2, CHalkyl and $C(alkyl)_2$;

U is selected from N and CR^2 where R^2 is selected from hydrogen, alkyl, halogens, amino, alkylamino, dialkylamino, nitro, cyano, alkoxy, aryloxy, thiol, alkylthiol, arylthiol and aryl;

V is selected from N and CR^3 where R^3 is selected from hydrogen, alkyl, halogens, alkyloxy, aryloxy and aryl;

and when a double bond exists between X and the ring atom to which Q is attached and Q is linked to the ring moiety by a single bond, X is selected from N, CH and CR^7, where R^7 is selected from alkyl, alkenyl, alkynyl and aryl; and

when a double bond links Q to the ring moiety and a single bond exists between X and the ring atom to which Q is attached, R^4 does not exist and X is NR^8, where R^8 is alkyl, alkenyl, alkynyl or aryl, except that when Y is N, U is CR^2 and V is CR^3, R^8 is not an alkyl or alkenyl group substituted at the fourth atom of the chain of said alkyl or alkenyl group, counted along the shortest route away from the ring moiety including any hetero atom present in said chain, by a member selected from OH, phosphate, diphosphate, triphosphate, phosphonate, diphosphonate, triphosphonate and pharmacologically acceptable salts, derivatives and prodrugs thereof;

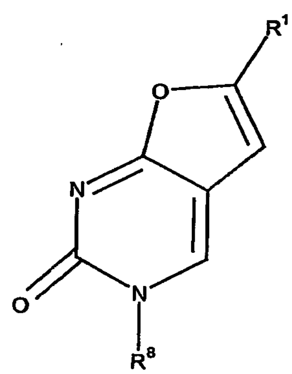
and pharmacologically acceptable salts, derivatives and prodrugs of compounds of formula (I).

Surprisingly the dideoxysugar in prior art compounds known from WO 01/85749 (structure 3 above) can be replaced by an alkyl, alkenyl, alkynyl or aryl moiety that does

not require phosphorylation for biological activity and hence does not require the hydroxy or any groups on the, for example, alkyl C_4 atom deemed necessary for phosphorylation.

Preferably neither R^4 nor R^8 contains any suitable hydroxy group that may be subject to biological phosphorylation. In particular, preferably neither R^4 nor R^8 is a ribose, deoxyribase, dideoxyribose, dideoxydidehydribose sugar or similar sugar group or close analogue.

Compounds having a double bond between X and the ring atom to which Q is attached are isomers of compounds having a single bond between X and the ring atom to which Q is attached. Compounds having a double bond between X and the ring atom to which Q is attached are entirely non-nucleosidic in nature. Examples of these two isomers are, for instance, structures 4 and 5:



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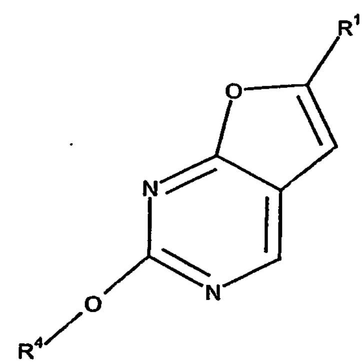

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Varying the composition of R^1, R^4 and R^8 of formula (I) determines the biological activity of the compounds.

Preferably Z is O or NH. Where Z is N-alkyl, suitably the alkyl is C_1 to C_5 alkyl.

Preferably Y is N.

Preferably Q is CH_2, S or O. More preferably Q is O. Where Q is N-alkyl, suitably the alkyl is C_1 to C_5 alkyl. Where Q is CHalkyl or $C(alkyl)_2$, suitably the alkyl is C_1 to C_5 alkyl.

Preferably each of U and V is CH.

When a double bond exists between X and the ring atom to which Q is attached, X and Y are preferably both N.

When a double bond exists between X and the ring atom to which Q is attached, Z is preferably O.

When a double bond exists between X and the ring atom to which Q is attached, Q is preferably O.

When X and Y are N, Q and Z are independently preferably selected from O, S and NH, more preferably Q and Z are O.

Throughout the present specification:

alkyl includes cycloalkyl, alkyl substituted with cycloalkyl, alkyl containing within the alkyl chain 1, 2, 3 or 4 heteroatoms selected independently from O, S and N, substituted alkyl and branched alkyl;

alkenyl includes cycloalkenyl, alkyl substituted with cycloalkenyl, alkenyl containing within the alkenyl chain 1, 2, 3 or 4 heteroatoms selected independently from O, S and N for example tetrahydrofuran (THF), substituted alkenyl and branched alkenyl;

alkynyl includes cycloalkynyl, alkyl substituted with cycloalkynyl, alkynyl containing within the alkynyl chain 1, 2, 3 or 4 heteroatoms selected independently from O, S and N, substituted alkynyl and branched alkynyl; and

aryl includes monocyclic and bicyclic fused 5, 6 and 7 membered aromatic rings, aryl containing 1, 2, 3 or 4 heteroatoms selected independently from O, S and N, alkylaryl for example benzyl, and substituted aryl and substituted alkylaryl for example substituted benzyl.

The nature, position and number of any substituents and unsaturation present in any alkyl, alkenyl, alkynyl and aryl group may be varied.

Examples of suitable substituents on any of said alkyl, alkenyl, alkynyl and aryl, including alkylaryl, groups include OH, halogens, amino, CN, COOH, CO_2alkyl(C_1 to C_5), $CONH_2$, CONHalkyl(C_1 to C_5), O-alkyl(C_1 to C_5), SH, S-alkyl(C_1 to C_5) and NO_2, and aryl(5 to 10 ring atoms), and with respect to aryl and alkylaryl groups include alkyl (C_1 to C_5), alkenyl (C_2 to C_5) and alkynyl (C_2 to C_5), wherein any of said alkyl, alkenyl, alkynyl and aryl moieties are each optionally substituted. Substituents on the said alkyl, alkenyl and alkynyl moieties, which are preferably straight chain, can be selected from the group comprising OH, halogens, amino, CN, SH and NO_2, and is preferably a halogen, more preferably chlorine. Where the said alkyl, alkenyl or alkynyl moiety is C_2 to C_5, the substituent is preferably at the terminus position. Substituents on the said aryl moiety can be selected from the group comprising OH, halogens, amino, CN, NO_2, and C_1 to C_{10} alkyl, which C_1 to C_{10} alkyl moiety is optionally substituted with a member selected from the group comprising OH, halogens, amino, CN, SH, NO_2. The said aryl moiety can comprise aryl or heteroaryl groups. Any ring heteroatoms may vary in position or number. Suitably 1, 2, 3 or 4 heteroring atoms may be present, preferably selected, independently, from O, N and S. The said aryl moiety can comprise one, or two fused, 5, 6 or 7 membered rings.

Preferably R^1 is selected from C_{3-20}alkyl, C_{3-20}cycloalkyl, C_{2-20}alkenyl, C_{3-20}alkynyl, C_{5-14} aryl and C_{1-10}alkylC_{5-14}aryl, more preferably C_{3-14}alkyl, C_{3-14}alkenyl, C_{3-14}alkynyl, more preferably C_{6-14}alkyl, C_{6-14}alkenyl, C_{6-14}alkynyl, even more preferably C_{8-10}alkyl, C_{8-10} alkenyl and C_{8-10}alkynyl.

Preferably R^1 is C_{4-14}alkyl, C_{4-14}alkenyl or C_{4-14}alkynyl, more preferably C_{4-12}alkyl, C_{4-12}alkenyl or C_{4-12}alkynyl, even more preferably C_{6-10}alkyl, C_{6-10}alkenyl or C_{6-10}alkynyl, even more preferably C_{8-10}alkyl, C_{8-10}alkenyl or C_{8-10}alkynyl.

Where there is a single bond between X and the ring atom to which Q is attached, R^1 is preferably C_{6-12}alkyl, C_{6-12}alkenyl or C_{6-12}alkynyl.

Where there is a double bond between X and the ring atom to which Q is attached, R^1 is preferably C_{4-12}alkyl, C_{4-12}alkenyl or C_{4-12}alkynyl.

Preferably R^1 is an alkyl group. Preferably R^1 is a straight chain alkyl group. Preferably R^1 is an unsubstituted alkyl group. Preferably R^1 is a saturated alkyl group.

Preferably R^1 is a C_7 to C_{13} alkyl group. More preferably R^1 is a C_8 to C_{12} alkyl group, even more preferably a C_9 to C_{11} alkyl group. Particularly preferred is R^1 being a C_9 or C_{10} alkyl group.

Where R^1 is a straight chain alkyl group, a preferred position for substitution is the terminus position.

Suitably any substituent in R^1 is non-polar, more suitably any such substituent is additionally hydrophobic. Preferred substituents on R^1 include halogen and O-alkyl(C_1 to C_5). Particularly preferred is O-alkyl with C_4, optionally terminally substituted with a halogen, preferably chlorine.

When R^1 is a cycloalkyl group, it suitably comprises 5 to 12 ring carbon atoms arranged in one or two adjoining rings.

Preferably R^1 is selected from the group comprising nC_4H_9, nC_6H_{13}, nC_7H_{15} and $nC_{10}H_{21}$. Preferably R^1 is $nC_{10}H_{21}$.

Preferably R^4 and R^8 are selected from C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{3-12}cycloalkyl, C_{1-6}alkyl substituted with C_{3-10}cycloalkyl, C_{5-14}aryl and C_{1-5}alkylC_{5-14}aryl.

Preferably R^4 and R^8 are selected from C_{1-10}alkyl C_{2-10}alkenyl, C_{2-10}alkynyl, C_1alkyl substituted with C_{5-6}cycloalkyl and C_1alkyl substituted with C_{5-7}aryl.

Even more preferably R^4 and R^8 are selected from C_{1-6}alkyl, C_{2-4}alkenyl, C_1alkyl substituted with C_{5-6}cycloalkyl and benzyl and substituted benzyl.

Preferably each of R^4 and R^8 are selected from the group comprising cycloC_5H_9, $CH(Et)_2$, nC_5H_{11}, 2-THF, CH_2cycloC_6H_{11}, 3-THF, cycloC_6H_{11}, C_3H_7, nC_4H_9, PhCH_2, TolCH_2, pMeOPhCH_2, CH_2cycloC_5H_9, Me and nC_3H_7.

Where a single bond exists between X and the ring atom to which Q is attached particularly preferred combinations of R^1 and R^8 are, respectively, nC_7H_{15} and cycloC_5H_9, nC_7H_{15} and $CH(Et)_2$, n$C_{10}H_{21}$ and 3-THF, n$C_{10}H_{21}$ and cycloC_6H_{11}, n$C_{10}H_{21}$ and C_3H_7, n$C_{10}H_{21}$ and CH_2cycloC_5H_9, nC_6H_{13} and Me, nC_6H_{13} and nC_3H_7, and nC_6H_{13} and PhCH_2. A particularly preferred combination is R^1 being n$C_{10}H_{21}$ and R^8 being CH_2cycloC_5H_9.

Where a double bond exists between X and the ring atom to which Q is attached particularly preferred combinations of R^1 and R^4 are, respectively, nC_4H_9 and cycloC_5H_9, nC_7H_{15} and cycloC_5H_9, nC_7H_5 and $CH(Et)_2$, nC_7H_{15} and nC_5H_{11} , n$C_{10}H_{21}$ and $CH(Et)_2$, n$C_{10}H_{21}$ and cycloC_6H_{11}, n$C_{10}H_{21}$ and nC_3H_7, n$C_{10}H_{21}$ and nC_4H_9, n$C_{10}H_{21}$ and PhCH_2, n$C_{10}H_{21}$ and CH_2cycloC_6H_{11}, n$C_{10}H_{21}$ and TolCH_2, n$C_{10}H_{21}$ and pMeOPhCH_2 , nC_6H_{13} and Me, nC_6H_{13} and nC_4H_9, and nC_6H_{13} and PhCH_2. Particularly preferred combinations are R^1 being n$C_{10}H_{21}$ with R^4 being any of nC_3H_7, nC_4H_9, PhCH_2, CH_2cycloC_6H_{11}, tolCH_2, and pMeOPhCH_2.

Suitably R^2 is selected from the group comprising H, C_1 to C_{10} alkyl, C_3 to C_{10} cycloalkyl, C_1 to C_{10} alkylamino, C_1 to C_{10} dialkylamino, C_1 to C_{10} alkyloxy, C_6 to C_{10} aryloxy, C_1 to C_{10} alkylthiol, C_6 to C_{10} arylthiol and C_6 to C_{10} aryl.

Suitably R^3 is selected from the group comprising H, C_1 to C_{10} alkyl, C_3 to C_{10} cycloalkyl, C_1 to C_{10} alkyloxy, C_6 to C_{10} aryloxy and C_6 to C_{10} aryl.

Preferably each of R^2 and R^3 is a small alkyl i.e. a C_1 to C_2 alkyl group or H. More preferably each of R^2 and R^3 is H.

Throughout the present specification "halogen" is taken to include any of F, Cl, Br and I.

Where not otherwise specified, alkyl is C_{1-6}alkyl, alkenyl is C_{2-6}alkenyl, alkynyl is C_{2-6}alkynyl, aryl is C_{5-14}aryl and alkylaryl is C_{1-6}alkylC_{5-14}aryl.

Where R^1, R^4 or R^8 is an aryl group, the group includes alkylaryl groups. Preferably R^1, R^4 and R^8 are C_{5-14}aryl groups or C_{1-4}alkylC_{5-14} aryl groups. Particularly preferred groups are benzyl and subtituted benzyl such as toluene (tol)CH_2, and pMeOPhCH_2. Preferred substituents include alkyl (C_{1-6}), alkoxy (C_{1-6}) and halogen (F, Cl, Br and I). The preferred substitution positions for phenyl and benzyl is para. Preferred aryl groups are C_6.

Where there is a single bond between X and the ring atom to which Q is attached:

when R^1 is alkyl, preferably R^1 is C_{6-12}alkyl;

when R^1 is alkynyl, preferably R^1 is C_8 or above alkynyl, more preferably C_{8-20}alkynyl, even more preferably C_{8-14}alkynyl; even more preferably C_{8-12}alkynyl; even more preferably C_{8-10}alkynyl;

when R^1 is aryl, preferably R^1 is a monocyclic or bicyclic fused 5, 6 or 7 membered ring, an aryl group containing 1, 2, 3 or 4 heteroatoms selected independently from O, S and N, alkylaryl for example benzyl, or substituted aryl or substituted alkylaryl for example substituted benzyl such as pMeOPhCH_2, more preferably a C_{5-14}aryl group or a C_{1-4}alkylC_{5-14} aryl group, even more preferably a C_6 aryl group, the substitutents being as set out above;

when R^1 is alkyl containing within the alkyl chain 1, 2, 3 or 4 heteroatoms selected independently from O, S and N, preferably R^1 is not a thioether, even more preferably R^1 being a thioether is excluded from the scope of formula (I); and/or

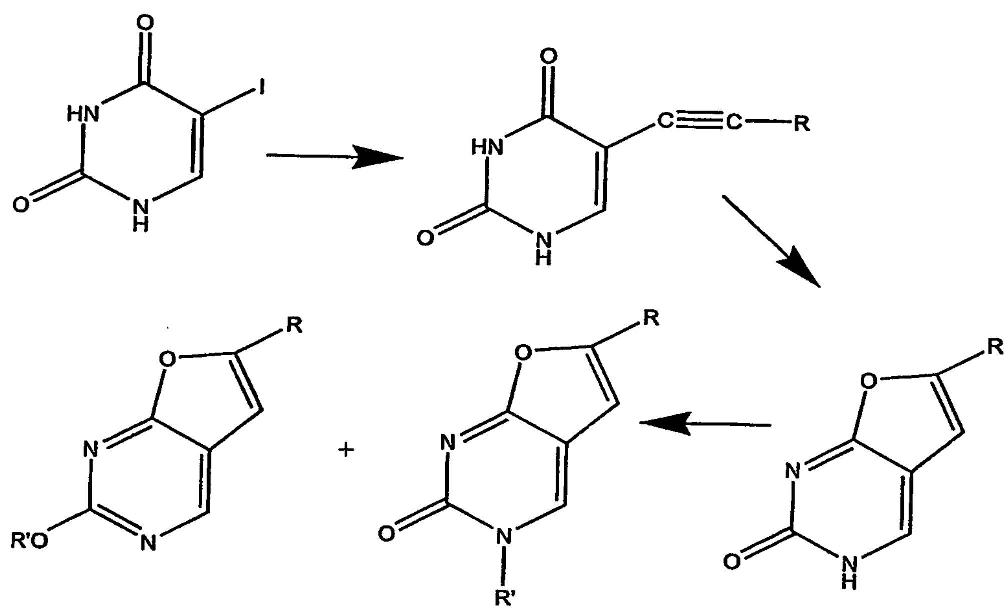
when R^8 is alkyl, R^8 is not methyl when R^1 is n-butyl, Y is N, Z is O and V and U are CH.

The preferred options recited immediately above with respect to there being a single bond between X and the ring atom to which Q is attached do not necessarily extend to those aspects of the present invention recited below directed, respectively, to: a compound according to the present invention for use in a method of treatment, suitably in the prophylaxis or treatment of a viral infection, preferably a cytomegalovirus infection; a method of prophylaxis or treatment of a viral infection, preferably a cytomegalovirus infection; and use of a compound of the present invention in the manufacture of a

medicament for use in the prophylaxis or treatment of a viral infection, particularly an infection with cytomegalovirus.

According to a further aspect of the present invention there is provided a method for preparing compounds having Formula I above wherein a 5-halo nucleoside analogue is contacted with a terminal alkyne in the presence of a catalyst. Alternatively 5-alkynyl nucleoside can be cyclised in the presence of a catalyst. Suitably the catalyst is a copper catalyst.

Compounds of the present invention may be prepared by a number of methods, which may for example involve a reaction scheme such as:



Thus, terminal acetylenes are coupled to 5-iodouracil under Pd catalysed conditions to give intermedaite 5-alkynyl compounds that may either be isolated or used in situ. These are cyclised under Cu catalysis to give bicyclic furano pyrimidines that are key synthons. These are alkylated to give mixtures of O and N alkyl products that can be readily separated.

The method of separation may include chromatography, precipitation, and crystallisation. The ratios of these products will vary, and need not be 1:1.

Compounds embodying the present invention can show anti-viral activity. In particular, it has surprisingly been found that compounds embodying the present invention can show antiviral activity against for example cytomegalovirus.

According to a further aspect of the present invention there is provided a compound according to the present invention for use in a method of treatment, suitably in the prophylaxis or treatment of a viral infection, preferably a cytomegalovirus viral infection.

According to a further aspect of the present invention there is provided a method of prophylaxis or treatment of viral infection, preferably a cytomegalovirus viral infection, comprising administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for use in the prophylaxis or treatment of a viral infection, particularly an infection with cytomegalovirus.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutially acceptable excipient.

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound of the present invention with a pharmaceutically acceptable excipient.

The compounds embodying the present invention present a number of advantages over existing agents for HCMV:

1. A novel non-nucleoside structure and possibly novel mechanism of action.
2. Antiviral activity at non-cytotoxic concentrations.
3. A lack of cross resistance with existing nucleoside drugs.

4. Useful physiochemical properties such as high lipophilicity. Lead structures have calculated logP (ClogP) values of Ca. 4-6.

The high lipophilicity of the present compounds may lead to improved *in vivo* dosing, tissue distribution and pharmacokinetics. In a preliminary rodent trial a compound with structure 5 with $R^1 = C_7H_{15}$ and R^4= cyclopentyl displayed significant bioavailability and half life following i.p. dosing. Moreover at a dose as high as 50mg/kg/day for 10 days no visible *in vivo* toxicity was noted, indicating a promising toxicology profile. Histology also revealed no detectable toxicity against brain, thymus, liver, lungs, kidney, breast, testi, ovum and spleen tissue.

The compounds embodying the present invention can be sufficiently lipophilic to warrant their formulation and use as non-p.o dosage forms including topical, transdermal and ocular formulations. The latter may be of particular value versus HCMV retinitis, common in persons co-infected with HIV. The agents would therein have significant dosing, tissue localisation and toxicology advantage over current agents.

The lack of chirality in structures embodying the present invention distinguishes them from typical nucleoside antivirals with possible costs of goods and ease of synthesis advantage.

The medicaments employed in the present invention can be administered by oral (p.o.) or parenteral (i.p.) routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, the compound of the invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and

calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The compounds of the invention may also be presented as liposome formulations.

In general a suitable dose will be in the range of 0.1 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 1 to 25 mg per kilogram body weight per day and most preferably in the range 5 to 10 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be

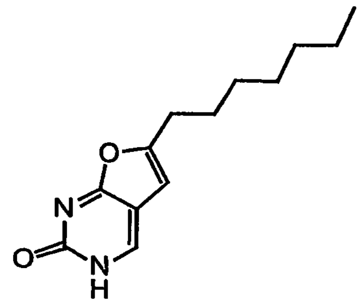
administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

Embodiments of the present invention will now be described by way of example only.

All reagents and solvents were obtained commercially and use without further purification, unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC) on DC-Alufolien $60F_{254}$ 0.2 mm plates. Compounds were visualised by UV fluorescence (wavelength 365 nm). The reaction mixtures were evaporated in a vacuum rotary evaporator (Büchi *Rotavapor* R-114) using the vacuum of a diaphragm pump. This process is referred to below as "evaporated/removed/distilled *in vacuo*" or "under reduced pressure". Flash column chromatography refers to the technique described by Still (Still *et al* J. Org. Chem. 1978, 43 (14), 2923-2925). The height of the silica gel 60 (220-440 mesh) in all cases was 15 cm. All air and moisture sensitive reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Reaction mixture temperatures were measured externally.

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX300 spectrometer at 300 MHz and 75.5 MHz respectively, with the corresponding deuterated solvents noted. The chemical shifts are reported in parts per million relative to the residual non-deuterated solvent peak (δ_H $CHCl_3$ 7.27; δ_H [D_5]DMSO 2.50; and δ_c $CHCl_3$ 77.0 and δ_c [D_5]DMSO 39.5 central peak). *J* values are given in Hz. The DEPT and NOE techniques were used to assign different carbon atoms. Chemical shifts are reported: value (splitting pattern, number of protons, coupling constant (where applicable), and assignment). Splitting pattern is designated as follows: s, singlet; app d, apparent doublet; d, doublet; dd, double doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; sept, septet; m, multiplet; and br, broad. Elemental analyses were carried out in the Microanalytical Laboratories of the School of Pharmacy, University of London.

6-Heptyl-3*H*-furo[2,3-*d*]pyrimidin-2-one (137)

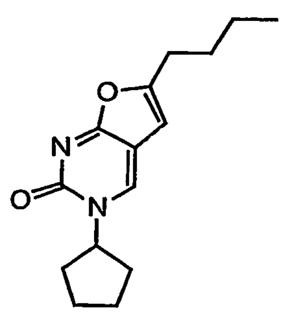


To a stirred solution of 5-Iodo-uracil (3.00 g, 12.60 mmol) in dry dimethylformamide (30 ml) at room temperature and under a nitrogen atmosphere, 1-hexyne (4.20 ml, 37.80 mmol), *tetrakis*(triphenylphosphine)palladium(0) (728 mg, 0.63 mmol), copper (I) iodide (240 mg, 1.26 mmol), and diisopropylethylamine (4.4 ml, 25.20 mmol), were added. The reaction mixture was stirred at room temperature for 19 hours, after which time TLC (chloroform/methanol 95:5) showed complete conversion of the starting material. Copper(I) iodide (240 mg, 1.26 mmol), triethylamine (20 ml) was added to the mixture which was subsequently refluxed for 8 hours. The reaction mixture was then concentrated *in vacuo*, and the product was purified by trituration with methanol, (1.20 g, 41%).

^{1}H-nmr (d_6-DMSO; 300 MHz): 11.97 (1H, bs, NH), 8.15 (1H, s, H-4) 6.37 (1H, s, H-5), 2.60 (2H, t, J = 7.3 Hz, α-CH_2), 1.62 (2H, m, CH_2), 1.28 (8H, m, 4 x CH_2), 0.86 (3H, t, J = 7.2 Hz, CH_3).

^{13}C-nmr unavailable due to solubility problems.

6-Butyl-3-cyclopentyl-3*H*-furo[2,3-*d*]pyrimidin-2-one (138) [Cf2158]



To a suspension of 6-Butyl-3*H*-furo[2,3-*d*]pyrimidin-2-one **(136)** (350 mg, 1.82 mmol) in dry DMF (20 ml) under an atmosphere of nitrogen, potassium carbonate (502 mg, 3.64 mmol) and cyclopentyl bromide (0,39 ml, 3.64 mmol) were added. The reaction mixture was stirred at 80 °C for one hour. The solvent was evaporated *in vacuo* and the residue was

dissolved in dichloromethane and extracted with a saturated solution of sodium chloride. The extracts were collected, dried on magnesium sulphate and evaporated to dryness. The crude product was purified by silica column chromatography, using chloroform as eluent, followed by a mixture of chloroform/methanol (97:3). The appropriate fractions were combined and the solvent was removed *in vacuo* to yield the product, which was further purified by trituration with diethyl ether, yielding the pure product (47 mg, 10%) as a white solid. Mp: 130-131 °C.

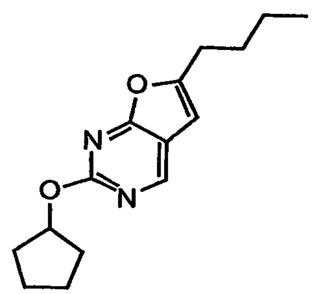
^{1}H-nmr ($CDCl_3$; 300 MHz): 7.84 (1H, s, H-4) 6.13 (1H, s, H-5), 5.29 (1H, m, CH), 2.69 (2H, t, J = 7.2 Hz, α-CH_2), 2.33 (2H, m, cyclopentyl-CH_2), 2.01-1.67 (8H, m, cyclopentyl + CH_2), 1.45 (2H, m, CH_2), 0.99 (3H, t, J = 7.3 Hz, CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.1 (CH_3), 22.5, 28.4, 29.3 (3 x CH_2), 24.5, 32.8 (cyclopentyl-CH_2), 59.6 (CH), 98.9 (C-5) 108.2 (C-4a), 135.6 (C-4), 156.2 (C-6), 160.3 (C-2), 171.3 (C-7a).

MS (ES+) m/e 283 (MNa^+, 100%)

Accurate mass: $C_{15}H_{20}N_2O_2Na$ requires 283.1422; found 283.1414.

6-Butyl-2-cyclopentyloxy-furo[2,3-*d*]pyrimidine (139) [Cf2159]



Also isolated from the above reaction as a white solid (270 mg, 57%). Mp: 69-71 °C.

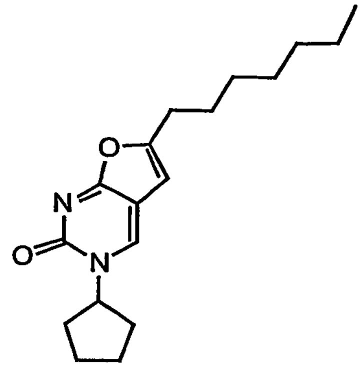
^{1}H-nmr ($CDCl_3$; 300 MHz): 8.61 (1H, s, H-4) 6.42 (1H, s, H-5), 5.48 (1H, m, CH), 2.78 (2H, t, J = 7.2 Hz, α-CH_2), 2.06-1.67 (10H, m, cyclopentyl + β-CH_2), 1.46 (2H, m, χ-CH_2), 0.99 (3H, t, J = 7.3 Hz, CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.2 (CH_3), 22.6, 28.4, 29.7 (3 x CH_2), 24.2, 33.2 (cyclopentyl-CH_2), 80.4 (CH), 99.5 (C-5) 113.9 (C-4a), 150.9 (C-4), 158.9 (C-6), 162.6 (C-2), 168.8 (C-7a).

MS (ES+) m/e 283 (MNa^+, 100%)

Accurate mass: $C_{15}H_{20}N_2O_2Na$ requires 283.1422; found 283.1428.

6-Heptyl-3-cyclopentyl-3*H*-furo[2,3-*d*]pyrimidin-2-one (140) [Cf2160]



This was synthesised as described for **138** above, using 350 mg of **137** (1.49 mmol) and 0.32 ml of cyclopentyl bromide (2.98 mmol). The product was collected as a white solid (88 mg, 20%). Mp: 142-143 °C.

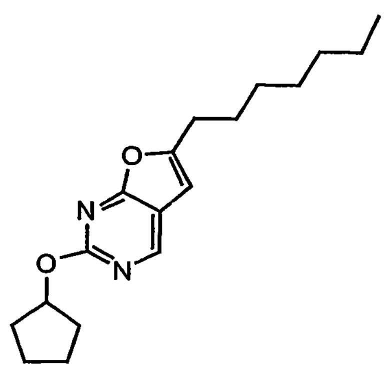
IR (KBr): 2930.6 (aliphatic), 1677.8 (CO amide).

^{1}H-nmr ($CDCl_3$; 300 MHz): 7.80 (1H, s, H-4) 6.09 (1H, s, H-5), 5.25 (1H, m, CH), 2.64 (2H, t, J = 7.4 Hz, α-CH_2), 2.25 (2H, m, cyclopentyl-CH_2), 1.90 -1.67 (8H, m, 4 x CH_2), 1.34 (8H, m, 4 x CH_2), 0.88 (3H, t, J = 6.7 Hz, CH_3). ^{13}C-nmr ($CDCl_3$; 75 MHz): 14.5 (CH_3), 23.0, 27.2, 27.9, 29.3, 29.7, 32.8 (6 x CH_2), 24.5, 33.1 (cyclopentyl-CH_2), 59.7 (CH), 98.9 (C-5) 108.2 (C-4a), 135.7 (C-4), 156.2 (C-6), 160.3 (C-2), 171.6 (C-7a).

MS (ES+) m/e 325 (MNa^+, 100%)

Accurate mass: $C_{18}H_{26}N_2O_2Na$ requires 325.1892; found 325.1883

6-Heptyl-2-cyclopentyloxy-furo[2,3-*d*]pyrimidine (141) [Cf2161]



Also isolated from the above reaction as a white solid (230 mg, 51%). Mp: 65-67 °C.

IR (KBr): 2954.1 (aliphatic), 1619.6 (C=N).

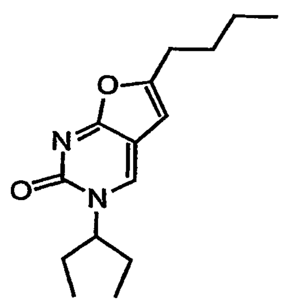
^{1}H-nmr ($CDCl_3$; 300 MHz): 8.60 (1H, s, H-4) 6.36 (1H, s, H-5), 5.48 (1H, m, CH), 2.77 (2H, t, J = 7.3 Hz, α-CH_2), 2.08-1.63 (10H, m, cyclopentyl + β-CH_2), 1.42-1.27 (8H, m, 4 x CH_2), 0.91 (3H, t, J = 7.2 Hz, CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.5 (CH_3), 23.0, 27.6, 28.8, 29.4, 29.4, 32.1 (6 x CH_2), 24.2, 33.2 (cyclopentyl-CH_2), 80.4 (CH), 99.5 (C-5) 113.9 (C-4a), 150.9 (C-4), 158.9 (C-6), 162.6(C-2), 168.8 (C-7a).

MS (ES+) m/e 325 (MNa^+, 100%)

Accurate mass: $C_{18}H_{26}N_2O_2Na$ requires 325.1892; found 325.1880

6-Butyl-3-(1-ethyl-propyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one (142) [Cf2194]



This was synthesised as described for **138** above, using 300 mg of **136** (1.56 mmol) and 0.40 ml of 3-bromopentane (3.12 mmol). The product was collected as a white solid (118 mg, 29%).

IR (KBr): 2958.1 (aliphatic), 1671.9 (CO amide).

^{1}H-nmr ($CDCl_3$; 300 MHz): 7.72 (1H, s, H-4) 6.14 (1H, s, H-5), 4.94 (1H, m, CH), 2.68 (2H, t, J = 7.4 Hz, α-CH_2), 1.93-1.66 (6H, m, 3 x CH_2), 1.43 (2H, m, CH_2), 1.00-0.88 (9H, m, 3 x CH_3).

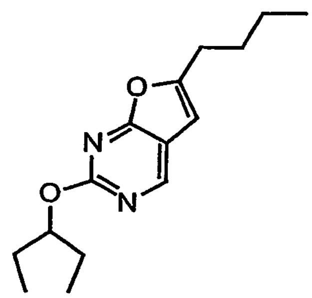
^{13}C-nmr ($CDCl_3$; 75 MHz): 10.7, 14.1 (3 x CH_3), 22.5, 27.9, 28.4, 29.3 (5 x CH_2), 61.3 (CH), 98.9 (C-5) 108.2 (C-4a), 135.4 (C-4), 156.7 (C-6), 160.3 (C-2), 171.4 (C-7a).

MS (ES+) m/e 285 (MNa^+, 100%)

Accurate mass: $C_{15}H_{22}N_2O_2Na$ requires 285.1579; found 285.1586

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67%; H, 8.45%; N, 10.68%. Found: C, 68.38%; H, 8.62%; N, 10.89%

6-Butyl-2-(1-ethyl-propoxy)-furo[2,3-*d*]pyrimidine (143) [Cf2193]



Also isolated from the above reaction as a white solid (171 mg, 42%).

IR (KBr): 2938.4 (aliphatic), 1620.0 (C=N).

^{1}H-nmr ($CDCl_3$; 300 MHz): 8.60 (1H, s, H-4) 6.35 (1H, s, H-5), 5.10 (1H, m, CH), 2.77 (2H, t, J = 7.4 Hz, α-CH_2), 1.91-1.70 (6H, m, 3 x CH_2), 1.43 (2H, m, CH_2), 1.00-0.90 (9H, m, 3 x CH_3).

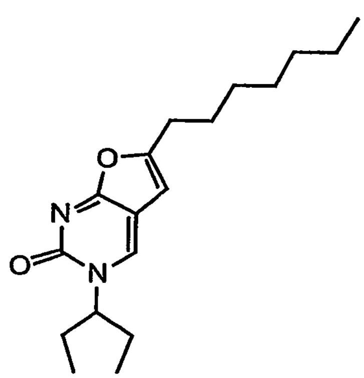
^{13}C-nmr ($CDCl_3$; 75 MHz): 10.0, 14.1 (3 x CH_3), 22.6, 26.5, 28.4, 29.7 (5 x CH_2), 80.0 (CH), 99.5 (C-5) 113.9 (C-4a), 150.9 (C-4), 158.9 (C-6), 162.9 (C-2), 168.8 (C-7a).

MS (ES+) m/e 285 (MNa^+, 100%)

Accurate mass: $C_{15}H_{22}N_2O_2Na$ requires 285.1579; found 285.1575

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67%; H, 8.45%; N, 10.68%. Found: C, 66.97%; H, 8.58%; N, 10.78%

6-Heptyl-3-(1-ethyl-propyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one (144) [Cf2190]



This was synthesised as described for **138** above, using 350 mg of **137** (1.50 mmol) and 0.40 ml of 3-bromopentane (3.00 mmol). The product was collected as a white solid (108 mg, 28%). Mp: 128-130 °C.

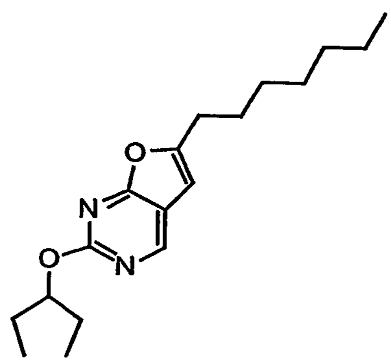
^{1}H-nmr ($CDCl_3$; 300 MHz): 7.71 (1H, s, H-4) 6.14 (1H, s, H-5), 4.94 (1H, m, CH), 2.68 (2H, t, J = 7.4 Hz, α-CH_2), 1.96-1.67 (6H, m, 3 x CH_2), 1.43-1.32 (8H, m, 4 x CH_2), 0.98-0.89 (9H, m, 3 x CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 10.7, 14.5 (3 x CH_3), 23.0, 27.2, 27.9, 28.7, 29.3 29.4, 32.1 (7 x CH_2), 61.3 (CH), 98.9 (C-5) 108.2 (C-4a), 135.4 (C-4), 156.7 (C-6), 160.3 (C-2), 171.4 (C-7a).

MS (ES+) m/e 327 (MNa^+, 100%), 305 (MH^+) (50%)

Accurate mass: $C_{18}H_{28}N_2O_2Na$ requires 327.2048; found 327.2038

6-Heptyl-2-(1-ethyl-propoxy)-furo[2,3-*d*]pyrimidine (145) [Cf2189]



Also isolated from the above reaction as a white solid (272 mg, 70%). Mp: 70-71 °C.

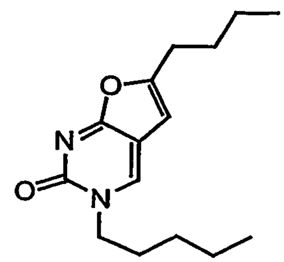
^{1}H-nmr ($CDCl_3$; 300 MHz): 8.48 (1H, s, H-4) 6.24 (1H, s, H-5), 5.01 (1H, m, CH), 2.65 (2H, t, J = 7.3 Hz, α-CH_2), 1.72-1.60 (6H, m, 3 x CH_2), 1.60-1.20 (8H, m, 4 x CH_2), 0.91-0.77 (9H, m, 3 x CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 9.9, 14.4 (3 x CH_3), 23.0, 26.4, 27.6, 28.7, 29.3, 29.4, 32.0 (7 x CH_2), 80.0 (CH), 99.5 (C-5) 113.9 (C-4a), 150.9 (C-4), 158.8 (C-6), 162.9 (C-2), 168.8 (C-7a).

MS (ES+) m/e 327 (MNa^+, 100%)

Accurate mass: $C_{18}H_{28}N_2O_2Na$ requires 327.2048; found 327.2053

6-Butyl-3-pentyl-3*H*-furo[2,3-*d*]pyrimidin-2-one (146) [Cf2195]



This was synthesised as described for **138** above, using 250 mg of **136** (1.30 mmol) and 515 mg of 1-Iodopentane (2.60 mmol). The product was collected as a white solid (133 mg, 40%). Mp: 139-141 °C.

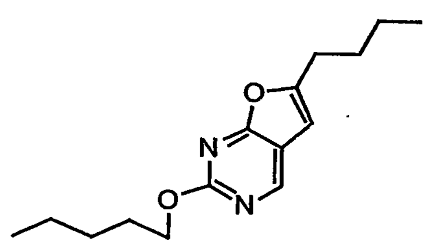
^{1}H-nmr ($CDCl_3$; 300 MHz): 7.77 (1H, s, H-4) 6.07 (1H, s, H-5), 3.96 (2H, t, J = 7.4 Hz, N-CH_2), 2.61 (2H, t, J = 7.4 Hz, α-CH_2), 1.94-1.58 (4H, m, 3 x CH_2), 1.43-1.24 (6H, m, 3 x CH_2), 0.93-0.84 (6H, m, 2 x CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.1, 14.3 (2 x CH_3), 22.5, 22.7, 28.4, 29.0, 29.2, 29.3 (6 x CH_2), 52.6 (N-CH_2), 98.8 (C-5) 108.1 (C-4a), 139.1 (C-4), 155.8 (C-6), 160.2 (C-2), 172.3 (C-7a).

MS (ES+) m/e 285 (MNa^+, 100%)

Accurate mass: $C_{15}H_{22}N_2O_2Na$ requires 285.1579; found 285.1568

6-Butyl-2-pentyloxy-furo[2,3-*d*]pyrimidine (147) [Cf 2327]



Also isolated from the above reaction as a white solid (62 mg, 20%). Mp: 51-52 °C.

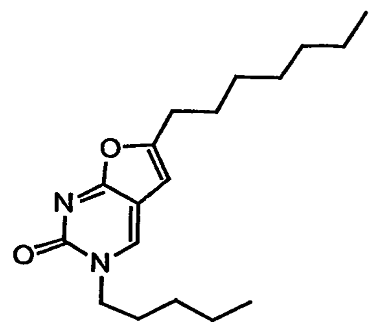
^{1}H-nmr ($CDCl_3$; 300 MHz): 8.49 (1H, s, H-4) 6.25 (1H, s, H-5), 4.32 (2H, t, J = 6.6 Hz, O-CH_2), 2.64 (2H, t, J = 7.3 Hz, α-CH_2), 1.85-1.66 (4H, m, 2 x CH_2), 1.43 (6H, m, 3 x CH_2), 0.92-0.73 (6H, m, 2 x CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.1, 14.4 (2 x CH_3), 22.5, 22.8, 28.4, 28.5, 28.9, 29.6 (7 x CH_2), 68.3 (O-CH_2), 99.5 (C-5) 114.1 (C-4a), 150.9 (C-4), 159.0 (C-6), 162.8 (C-2), 168.8(C-7a).

MS (ES+) m/e 285 (MNa^+, 100%)

Accurate mass: $C_{15}H_{22}N_2O_2Na$ requires 285.1579; found 285.1584

6-Heptyl-3-pentyl-3*H*-furo[2,3-*d*]pyrimidin-2-one (148) [Cf2192]



This was synthesised as described for **138** above, using 350 mg of **137** (1.50 mmol) and 594 mg of 1-Iodopentane (3.00 mmol). The product was collected as a white solid (207 mg, 45%). Mp: 161-162 °C.

IR (KBr): 2922.1 (aliphatic), 1678.3 (CO amide).

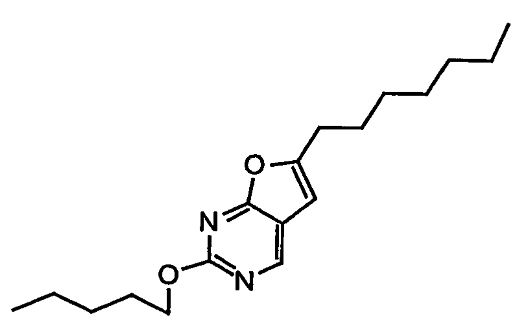
^{1}H-nmr ($CDCl_3$; 300 MHz): 7.87 (1H, s, H-4) 6.18 (1H, s, H-5), 4.07 (2H, t, J = 7.4 Hz, N-CH_2), 2.71 (2H, t, J = 7.3 Hz, α-CH_2), 1.93-1.71 (4H, m, 2 x CH_2), 1.42 (12H, m, 6 x CH_2), 0.98 (6H, m, 2 x CH_3).

^{13}C-nmr ($CDCl_3$; 75 MHz): 14.3, 14.9 (2 x CH_3), 22.7, 23.0, 27.2, 28.7, 29.1, 29.3, 29.3 29.4 32.1 (9 x CH_2), 52.6 (N-CH_2), 98.8 (C-5) 108.1 (C-4a), 139.1 (C-4), 155.8 (C-6), 160.3 (C-2), 172.3 (C-7a).

MS (ES+) m/e 327 (MNa^+, 100%)

Accurate mass: $C_{18}H_{28}N_2O_2Na$ requires 327.2048; found 327.2042

6-Heptyl-2-pentyloxy-furo[2,3-*d*]pyrimidine (149) [Cf2191]

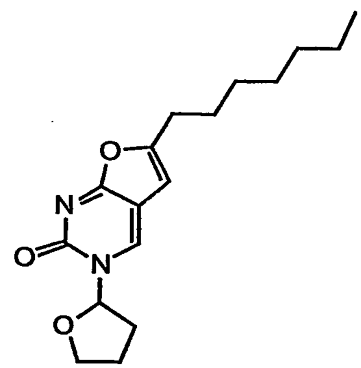


Also isolated from the above reaction as a white solid (141 mg, 31%). Mp: 48-49 °C.
IR (KBr): 2933.0 (aliphatic), 1618.0 (C=N).
^{1}H-nmr ($CDCl_3$; 300 MHz): 8.50 (1H, s, H-4) 6.25 (1H, s, H-5), 4.30 (2H, t, J = 6.7 Hz, O-CH_2), 2.65 (2H, t, J = 7.4 Hz, α-CH_2), 1.80-1.60 (4H, m, 2 x CH_2), 1.44-1.19 (12H, m, 6 x CH_2), 0.86-0.77 (6H, m, 2 x CH_3).
^{13}C-nmr ($CDCl_3$; 75 MHz): 14.4 (2 x CH_3), 22.8, 23.0, 27.6, 28.5, 28.7, 28.9, 29.3, 29.4, 32.0 (9 x CH_2), 68.3 (O-CH_2), 99.5 (C-5) 114.1 (C-4a), 150.8 (C-4), 159.0 (C-6), 162.8 (C-2), 172.3 (C-7a).

MS (ES+) m/e 327 (MNa^+, 100%)

Accurate mass: $C_{18}H_{28}N_2O_2Na$ requires 327.2048; found 327.2050

6-Heptyl-3-(tetrahydro-furan-2-yl)-3*H*-furo[2,3-*d*]pyrimidin-2-one (154) [Cf2196]



To a suspension of 6-heptyl-3*H*-furo[2,3-*d*]pyrimidin-2-one **(137)** (288 mg, 1.23 mmol) in dry DMF (10 ml) 2-tert-Butoxytetrahydrofuran (709 mg, 4.92 mmol) was added. The reaction mixture was stirred at 150°C for 10 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in dichloromethane and purified by silica column chromatography, using chloroform as eluent, followed by a mixture of chloroform/methanol (98:2). The appropriate fractions were combined and the solvent was removed *in vacuo* to yield the product, which was further purified by trituration with diethyl ether, yielding the pure product (150 mg mg, 40%) as a white solid.
IR (KBr): 2927.1 (aliphatic), 1671.9 (CO amide), 1084.0 (C-O).
^{1}H-nmr ($CDCl_3$; 300 MHz): 7.93 (1H, s, H-4) 6.09 (2H, m, H-5 and H-1'), 4,26 and 4,04 (2H, m, H-5'), 2.60 (2H, t, J = 7.4 Hz, α-CH_2), 2.56 (2H, m, H-2'$_a$), 2.18 and 2.00 (2H, m, H-3') 1.99 (2H, m, H-2'$_b$), 1.59 (2H, m, CH_2), 1.30-1.23 (8H, m, 4 x CH_2), 0.83 (3H, t, J = 6.7 Hz, CH_3).

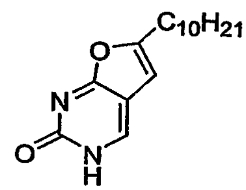
^{13}C-nmr ($CDCl_3$; 75 MHz): 14.5 (CH_3), 23.0, 23.7. 27.2, 28.7, 29.3, 29.4, 32.1, 33.8 (8 x CH_2), 71.1 (C-5'), 90.2 (C-1'), 99.1 (C-5), 107.6 (C-4a), 134.2 (C-4), 155.2 (C-6), 160.2 (C-2), 171.3 (C-7a).

MS (ES+) m/e 327 (MNa^+, 100%)

Accurate mass: $C_{17}H_{24}N_2O_3Na$ requires 327.1685; found 327.1678

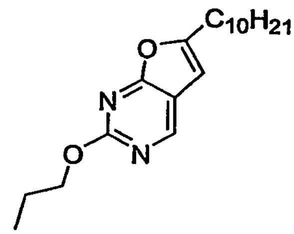
Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08%; H, 7.95%; N, 9.20%. Found: C, 67.01%; H, 8.14%; N, 9.26%

6-Decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one 26



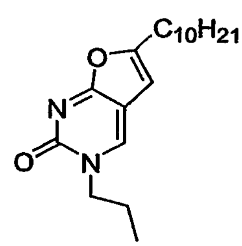
To a dry DMF (50 mL) solution of 5-iodouracil **23** (5.00 g, 21 mmol), tetrakis(triphenylphosphine)palladium(0) (1.00 g, 0.87 mmol, 0.04 equiv.) and copper iodide (0.80 g, 4.2 mmol, 0.2 equiv.) under a nitrogen atmosphere was added dry DIPEA (7.3 mL, 5.42 g, 42 mmol, 2 equiv.) and 1-dodecyne **24** (13.5 mL, 10.48 g, 63 mmol, 3 equiv.) *via* syringe with stirring. The initially opaque yellow solution proceeded to change colour on stirring at room temperature to a clear dark yellow solution, and eventually an opaque dark green suspension formed after a couple of hours. The suspension was allowed to react at RT with stirring for 18 h. TLC analysis of the resulting mixture indicated that most of the starting material had reacted, and the presence of a blue fluorescent spot was clearly observed. Dry triethylamine (25 mL) and a further addition of copper iodide (0.80 g) was then made to the suspension, and the resultant reaction mixture heated to 80 °C for 6 h with stirring under N_2. The suspension was allowed to cool to RT overnight with stirring. The resultant precipitate was collected by suction filtration, and washed consecutively with methanol and DCM. The collected solid was triturated in hot methanol to yield *the title compound* **26** as a white insoluble solid of weight 3.79 g (65 % from 23).

6-Decyl-2-propoxy-furo[2,3-*d*]pyrimidine Cf2303



26 (0.30 g, 1.086 mmol), potassium carbonate (0.30 g, 2.17 mmol, 2 equiv) and 1-iodopropane (**30**, 0.22 mL, 2.17 mmol, 2 equiv.) were suspended in dry DMF (5 mL) under N_2, and the reaction mixture heated to 100 °C with stirring overnight. The solvent was then removed *in vacuo* at 80 °C, and the crude mixture purified by flash chromatography in a 0-5 % methanol/DCM eluent gradient to yield **31** (102 mg, 29 %), *the title compound*, as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H, 4-H), 6.49 (s, 1H, 5-H), 4.44 (t, J = 6.7 Hz, 2H, O-CH_2-), 2.81 (t, J = 7.6 Hz, 2H, 1'-CH_2), 1.95 (app sex, J = 7.1 Hz, 2H, CH_2), 1.82 (m, J = 6.6 Hz, 2H, CH_2), 1.43 (m, 14H, CH_2), 1.15 (t, J = 7.4 Hz, 3H, O-CH_2CH_3), 0.97 (t, J = 7.0 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9 (7a-C), 162.9 (2-C), 159.1 (6-C), 150.9 (4-CH), 114.2 (4a-C), 99.5 (5-CH), 69.9 (O-CH_2), 32.3 (1'-CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 14.5 (O-CH_2CH_3), 10.9 (-CH_2CH_3).

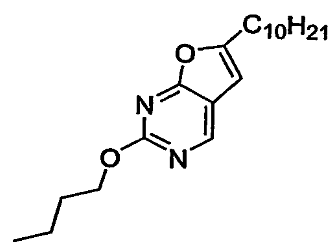
6-Decyl-3-propyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2304



Also isolated from the mix was 191 mg of *the title compound* **32** (55 % yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.74(s, 1H, 4-H), 6.13(s, 1H, 5-H), 4.01 (t, J = 7.3 Hz, 2H, N-CH_2-), 2.70 (t, J = 7.7 Hz, 2H, 1'-CH_2), 1.89 (app sex, J = 7.4 Hz, 2H, CH_2), 1.89 (m, J = 7.4 Hz, 2H, CH_2), 1.70 (m, J = 7.4 Hz, 2H, CH_2), 1.38 (m, 14H, CH_2), 1.04 (t, J = 7.4 Hz, 3H, N-CH_2CH_3), 0.96 (t, J = 7.0 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 169.9 (7a-C), 160.4 (2-C), 156.1 (6-C), 138.9 (4-CH), 108.6 (4a-C), 98.6 (5-CH), 54.2 (N-CH_2), 32.3

(1'-CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 14.5 (O-CH_2CH_3), 11.5 (-CH_2CH_3).

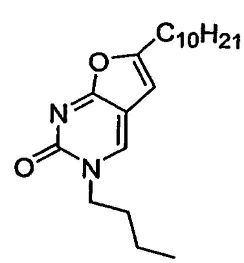
2-Butoxy-6-decyl-furo[2,3-*d*]pyrimidine Cf2305



26 (0.30 g, 1.086 mmol), potassium carbonate (0.30 g, 2.17 mmol, 2 equiv) and 1-iodobutane **33** (0.25 mL, 2.17 mmol, 2 equiv.) were suspended in dry DMF (5 mL) under N_2, and the reaction mixture heated to 100 °C with stirring overnight. The solvent was then removed *in vacuo* at 80 °C, and the crude mixture purified by flash chromatography in a 0-5 % methanol/DCM eluent gradient to yield **34** (114 mg, 32 %) as white solid.

^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H, 4-H), 6.36 (s, 1H, 5-H), 4.36 (t, J = 6.7 Hz, 2H, O-CH_2-), 2.75 (t, J = 7.6 Hz, 2H, 1'-CH_2), 1.90-1.74 (m, 4H, CH_2), 1.54 (m, 2H, CH_2), 1.29 (m, 14H, CH_2), 1.00 (t, J = 6.8 Hz, 3H, O-CH_2CH_3), 0.91 (t, J = 7.0 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9 (7a-C), 162.9 (2-C), 159.1 (6-C), 150.9 (4-CH), 113.9 (4a-C), 99.5 (5-CH), 68.1 (O-CH_2), 32.3 (1'-CH_2), 31.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 23.1 (CH_2), 19.6 (CH_2), 14.5 (O-CH_2CH_3), 14.2 (-CH_2CH_3).

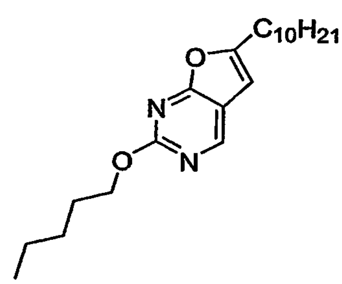
3-Butyl-6-decyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2306



Also isolated from the mixture was *the title compound* **35** (205 mg, 57 % yield) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H, 4-H), 6.04 (s, 1H, 5-H), 3.93 (t, J = 7.4 Hz, 2H, N-CH_2-), 2.56 (t, J = 7.4 Hz, 2H, 1'-CH_2), 1.71 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.36-1.18 (m, 16H, CH_2), 0.88 (t, J = 7.2 Hz, 3H, N-CH_2-CH_3), 0.80 (t, J = 6.5 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 172.3 (7a-C), 160.3 (2-C), 155.9 (6-C), 139.2 (4-CH), 108.2 (4a-C), 98.8 (5-CH), 52.4 (N-CH_2-), 32.3 (1'-CH_2), 31.6 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 20.2 (CH_2), 14.5 (O-CH_2CH_3), 14.1 (-CH_2CH_3).

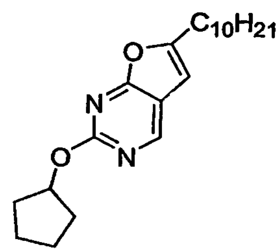
6-Decyl-2-pentyloxy-2,3-dihydrofuro[2,3-*d*]pyrimidine Cf2247



6-Decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one **26** (200 mg, 0.72 mmol), potassium carbonate (199 mg, 1.44 mmol, 2 equiv.) and 1-iodopentane **36** (0.2 mL, 2 equiv.) were suspended in dry DMF (8 mL) under N_2, and the suspension heated to 120 °C with stirring for 4 h. The solvent was removed *in vacuo* at 80 °C, with subsequent additions and removals of toluene (2 mL) to eliminate DMF traces. The crude residue was purified by flash column chromatography to yield **37** (88 mg, 35 %) as a cream solid.

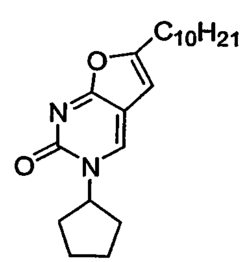
^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H, 4-H), 6.33 (s, 1H, 5-H), 4.38 (t, 2H, J = 6.7 Hz, 1'-CH_2), 2.73 (t, 2H, J = 7.4 Hz, α-CH_2), 1.84 (qt, 2H, J = 6.8 Hz, CH_2), 1.74 (m, 2H, CH_2), 1.50-1.26 (m, 18H, 9 x CH_2), 0.94-0.85 (m, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9 (7a-C), 162.9 (2-C), 159.1 (6-C), 150.9 (4a-C), 99.5 (5-CH), 68.4 (1'-CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.4 (CH_3). Elemental analysis calcd for $C_{21}H_{34}N_2O_2$ (346.5): C 72.79, N 8.08, H 9.89; found C 73.68, N 10.03, H 8.06.

2-Cyclopentyloxy-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidine Cf2250



26 (1.00 g, 3.62 mmol), potassium carbonate (1.00 g, 7.24 mmol, 2 equiv.) and cyclopentyl bromide **39** (0.23 mL, 2.17 mmol, 2 equiv.) were suspended in dry DMF (15 mL) under N_2, and the mixture stirred at RT for 6 h. The grey/green suspension was then heated to 120 °C for 5 h, then allowed to cool with stirring overnight. The solvent was removed *in vacuo* at 80 °C. The crude residue was purified by flash column chromatography in 0-1% MeOH/DCM eluent gradient to yield **40** as a white solid (0.87 g, 70 % yield). ^{1}H NMR ($CDCl_3$) δ 8.48 (b, 1H, 4-H), 6.23 (s, 1H, 5-H), 5.36 (m, 1H, 1'-H), 2.65 (t, 2H, J = 7.5 Hz, α-CH_2), 1.93-1.52 (m, 10H, 5 x CH_2), 1.25-1.17 (m, 14H, 7 x CH_2), 0.78 (t, 3H, J = 6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ = 168.8 (7a-C), 162.5 (2-C), 158.9 (6-C), 150.9 (4-CH), 113.9 (4a-C), 99.5 (5-CH), 80.3 (1'-CH), 33.1 (2 x CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.6 (2 x CH_2), 24.2 (CH_2), 23.1 (CH_2), 14.5 (CH_3). Elemental analysis calculated for $C_{21}H_{32}N_2O_2$ (344.5): C 73.22, N 8.13, H 9.36; found C 73.85, N 8.61, H 9.84.

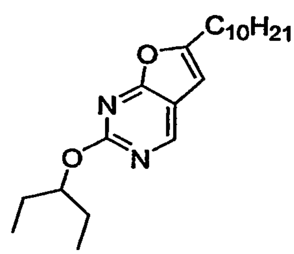
3-Cyclopentyl-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one Cf2251



Also isolated from the above reaction was *the title compound* **41** (0.18 g, 14 %) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H, 4-H), 6.05 (s, 1H, 5-H), 5.16 (m, 1H, 1'-H), 2.56 (t, 2H, *J* = 7.5 Hz, α-CH_2), 2.16 (m, 2H, CH_2), 1.82-1.55 (m, 8H, 4 x CH_2), 1.25-1.19 (m, 14H, 7 x CH_2), 0.80 (t, 3H, *J* = 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.6 (7a-C), 160.3 (6-C), 156.2 (2-C), 135.8 (4-CH), 108.3 (4a-C), 99.0 (5-CH), 59.7 (1'-CH_2), 32.8 (2 x CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.2 (2 x CH_2), 24.5 (CH_2), 23.1 (CH_2), 14.5 (CH_3). Elemental analysis calculated for $C_{21}H_{32}N_2O_2$ (344.5): C 73.22, N 8.13, H 9.36; found C 72.83, N 8.18, H 9.84.

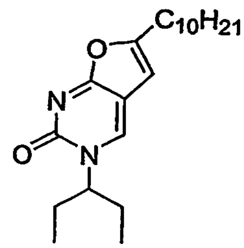
2-(1'-Ethyl-propyloxy)-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidine Cf2252



26 (0.50 g, 1.81 mmol), potassium carbonate (0.50 g, 3.62 mmol, 2 equiv) and 3-bromopentane **42** (0.45 mL, 3.62 mmol, 2 equiv.) were suspended in dry DMF (15 mL) under N_2, and the reaction mixture heated to 120 °C with stirring for 150 min. The dark suspension was allowed to cool to RT over 2 h, and then the solvent was removed under reduced pressure at 80 °C. The residue was then subjected to flash column chromatography purification in a 0-5 % MeOH/DCM eluent gradient to yield **43** as a yellow oil of weight 0.27 g (43 % yield).

^{1}H NMR ($CDCl_3$) δ = 8.44 (s, 1H, 4-H), 6.20 (s, 1H, 5-H), 4.96 (qt, 1H, *J* = 6.0 Hz, 1'-H), 2.60 (t, 2H, *J* = 7.5 Hz, α-CH_2), 1.68-1.55 (m, 6H, 3 x CH_2), 1.24-1.13 (m, 12H, 6 x CH_2), 0.84 (t, 6H, *J* = 7.4 Hz, 2 x CH_3), 0.74 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ = 168.8 (7a-C), 162.9 (6-C), 158.7 (2-C), 150.9 (4-CH), 113.9 (4a-C), 99.5 (5-CH), 79.9 (1'-CH), 32.2 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 26.7 (2 x CH_2), 26.4 (CH_2), 23.0 (CH_2), 14.4 (CH_3), 9.9 (2 x CH_3). Elemental analysis calcd for $C_{21}H_{34}N_2O_2$ (346.5): C 72.79, N 8.08, H 9.89; found C 73.12, N 8.56, H 9.93.

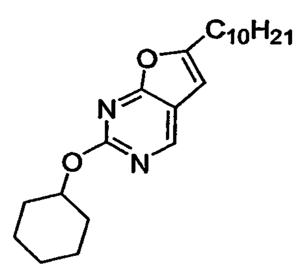
3-(1'-Ethyl-propyl)-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one Cf2253



Also isolated from the above reaction was *the title compound* **44** as a white solid (0.168 g, 27 %).

[1]H NMR ($CDCl_3$) δ = 7.72 (s, 1H, 4-H), 6.15 (s, 1H, 5-H), 4.94 (b, 1H, 1'-H), 2.67 (t, 2H, J = 7.4 Hz, α-CH_2), 1.87 (m, 2H, CH_2), 1.71 (m, 4H, 2 x CH_2), 1.36-1.23 (m, 14H, 7 x CH_2), 0.91 (t, 9H, J = 6.8 Hz, 3 x CH_3); [13]C NMR ($CDCl_3$) δ = 171.2 (7a-C), 160.4 (6-C), 156.7 (2-C), 135.5 (4-CH), 108.3 (4a-C), 98.9 (5-CH), 32.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (2 x CH_2), 29.5 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 14.5 (CH_3), 10.8 (2 x CH_3). Elemental analysis calculated for $C_{21}H_{34}N_2O_2$ (346.5): C 72.79, N 8.08, H 9.89; found C 72.65, N 8.16, H 10.08.

2-Cyclohexyloxy-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidine Cf2294

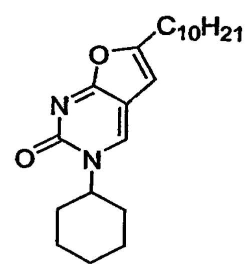


26 (300 mg, 1.086 mmol) and potassium carbonate (299 mg, 2.17 mmol, 2 equiv.) were suspended in dry DMF (10 mL) and cyclohexyl bromide **45** (0.54 mL, 2.17 mmol, 2 equiv.) added *via* syringe under N_2. The suspension was heated with stirring to 100 °C overnight. The solvent was removed *in vacuo* at 80 °C. The residue was suspended in DCM and washed with water. The organic layer was dried over $MgSO_4$, the solvent distilled *in vacuo* and the resultant residue purified by flash column chromatography in a 0-

2 % MeOH/DCM eluent gradient to yield **46** as a clear colourless waxy solid (78 mg, 20 % yield).

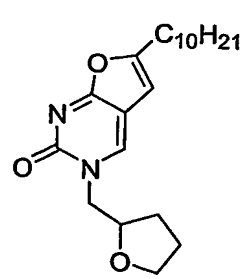
^{1}H NMR ($CDCl_3$) δ = 8.68 (s, 1H, 4-H), 6.43 (s, 1H, 5-H), 5.16 (m, 1H, 1'-H), 2.85 (t, 2H, J = 7.4 Hz, α-CH_2), 2.19 (m, 2H, CH_2), 1.94 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.58-1.32 (m, 18H, 9 x CH_2), 0.99 (t, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9 (7a-C), 162.3 (2-C), 158.9 (6-C), 151.0 (4-*C*H), 114.0 (4a-C), 99.6 (5-*C*H), 75.8 (1'-*C*H), 32.3 (*C*H_2), 32.0 (*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (2 x *C*H_2), 29.5 (*C*H_2), 28.8 (*C*H_2), 27.6 (*C*H_2), 26.0 (*C*H_2), 24.3 (2 x *C*H_2), 23.1 (*C*H_2), 14.6 (*C*H_3).

3-Cyclohexyl-6-decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one Cf2295



Also isolated from the above reaction was *the title compound* **47** (23 mg, 6 %) as a white solid. ^{1}H NMR ($CDCl_3$) 7.86 (s, 1H, 4-H), 6.13 (s, 1H, 5-H), 4.90 (m, 1H, 1'-H), 2.68 (t, 2H, J = 7.4 Hz, α-CH_2), 2.09-1.30 (m, 26H, 13 x CH_2), 0.93 (t, 3H, J = 6.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.5 (7a-C), 160.3 (2-C), 155.8 (6-H), 135.6 (4-*C*H), 108,1 (4a-C), 98.9 (5-*C*H), 57.1 (1'-*C*H), 33.3 (*C*H_2), 32.3 (*C*H_2), 32.0 (2 x *C*H_2), 29.7 (2 x *C*H_2), 26.2 (*C*H_2), 25.8 (*C*H_2), 24.3 (*C*H_2), 23.1 (*C*H_2), 14.6 (*C*H_3).

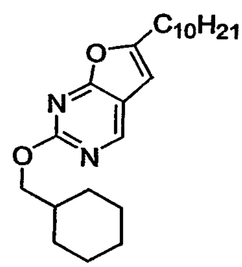
6-Decyl-3-(tetrahydro-furan-2-ylmethyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one 72 Cf2309



The title compound **72** (157 mg, 42 %) was also isolated from the reaction mixture as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H, 4-H), 6.13 (s, 1H, 5-H), 4.55 (dd, J = 2.3, 13.6 Hz, 1H, N-*CH*$_2$-THF), 4.29 (m, 1H, N-*CH*$_2$-THF), 3.93-3.72 (m, 3H, THF-*CH*), 2.68 (t, J = 7.4 Hz, 2H, 1'-*CH*$_2$), 2.26-2.15 (m, 1H, THF-*CH*), 2.00-1.90 (m, 2H, *CH*$_2$), 1.71-1.63 (m, 3H, THF-*CH*), 1.37-1.31 (m, 14H, *CH*$_2$), 0.93 (t, J = 6.4 Hz, 3H, *CH*$_3$); ^{13}C NMR ($CDCl_3$) δ 172.4 (7a-C), 160.2 (2-C), 156.1 (6-C), 140.5 (4-*C*H), 107.9 (4a-C), 98.9 (5-*C*H), 77.3 (THF-*C*), 68.6 (THF-*C*), 54.9 (N-1'-CH$_2$-THF), 32.3 (*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.5 (*C*H$_2$), 29.2 (*C*H$_2$), 28.7 (*C*H$_2$), 27.2 (*C*H$_2$), 26.2 (*C*H$_2$), 23.1 (*C*H$_2$), 14.6 (-CH$_2$*C*H$_3$).

2-Cyclohexylmethoxy-6-decyl-furo[2,3-*d*]pyrimidine Cf2274

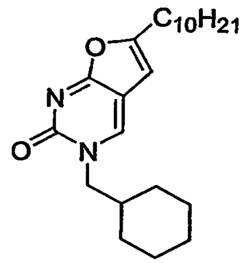


26 (0.30 g, 1.086 mmol) and potassium carbonate (0.30 g, 2.17 mmol, 2 equiv) were suspended in dry DMF (10 mL) under N_2, and (bromomethyl)cyclohexane **48** (0.30 mL, 2.17 mmol, 2 equiv.) added *via* syringe to the resultant stirred suspension. The suspension was then heated to 120 °C with stirring for 3 h, then allowed to cool with stirring overnight. The solvent was then removed *in vacuo* at 80 °C, and the crude mixture purified by flash chromatography in a 0-2% methanol/DCM eluent gradient to yield **49** (189 mg, 47 %) as white solid.

^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H, 4-H), 6.67 (s, 1H, 5-H), 4.35 (d, J = 6.2 Hz, 2H, O-*CH*$_2$-CyHx), 2.79 (t, J = 7.4 Hz, 2H, 1'-*CH*$_2$), 1.97-1.90 (m, 3H, CyHx-*CH*), 1.78 (m, 6H, CyHx-*CH*), 1.38-1.31 (m, 16H, *CH*$_2$), 1.19-1.08 (m, 2H, CyHx-*CH*), 0.91 (t, J = 6.4 Hz, 3H, -CH$_2$*CH*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.9 (7a-C), 163.0 (2-C), 159.1 (6-C), 150.9 (4-*C*H), 114.2 (4a-C), 99.5 (5-*C*H), 73.6 (O-CH$_2$-CyHx), 37.7 (CyHx-*C*), 32.3 (1'-*C*H$_2$), 30.2

(CyHx-*C*), 30.0 (2 X CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 26.2 (2 X CH_2), 23.1 (CH_2), 14.6 (-CH_2CH_3).

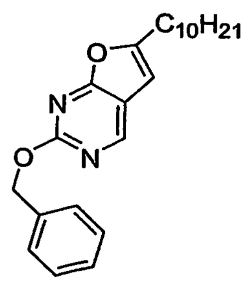
3-Cyclohexylmethyl-6-decyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2275



Also isolated from the mix as a white solid in a yield of 33 % (129 mg) was *the title compound* **50.**

[1]H NMR ($CDCl_3$) δ 7.72 (s, 1H, 4-H), 6.12 (s, 1H, 5-H), 3.64 (d, J = 7.3 Hz, 2H, N-CH_2-CyHx), 2.66 (t, J = 7.5 Hz, 2H, 1'-CH_2), 2.04-1.95 (m, 1H, CyHx-C*H*), 1.94-1.68 (m, 6H, CyHx-C*H*), 1.35-1.29 (m, 16H, CH_2), 1.23 (m, 2H, CyHx-C*H*), 1.02 (m, 2H, CyHx-C*H*), 0.90 (t, J = 6.4 Hz, 3H, -CH_2CH_3); [13]C NMR ($CDCl_3$) δ 172.3 (7a-C), 160.3 (2-C), 156.0 (6-C), 139.7 (4-*C*H), 107.7 (4a-C), 98.7 (5-*C*H), 58.8 (N-CH_2-CyHx), 36.9 (CyHx-*C*), 32.3 (1'-CH_2), 30.9 (CyHx-*C*), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 26.0 (2 X CH_2), 23.1 (CH_2), 14.6 (-CH_2CH_3).

2-Benzyloxy-6-decyl-furo[2,3-*d*]pyrimidine Cf2307

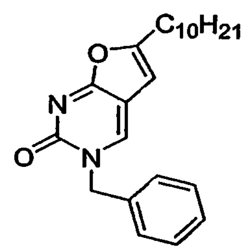


26 (0.30 g, 1.086 mmol), potassium carbonate (0.30 g, 2.17 mmol, 2 equiv) and benzyl chloride (**51**, 0.25 mL, 2.17 mmol, 2 equiv.) were suspended in dry DMF (5 mL) under N_2,

and the reaction mixture heated to 100 °C with stirring overnight. The solvent was then removed *in vacuo* at 80 °C, and the crude mixture purified by flash chromatography in a 0-5 % methanol/DCM eluent gradient to yield **52** (54 mg, 14 %) as white solid.

^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1H, 4-H), 7.57 (d, *J* = 6.7 Hz, 2H, Ar-C*H*), 7.36 (m, 3H, Ar-C*H*), 6.40 (s, 1H, 5-H), 5.54 (s, 2H, O-CH_2-Ph), 2.78 (t, *J* = 7.2 Hz, 2H, 1'-CH_2), 1.79 (m, 2H, CH_2), 1.32 (m, 14H, CH_2), 0.92 (m, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.5 (2-C), 159.4 (6-C), 150.9 (4-*C*H), 137.0 (Ar-*C*), 128.8 (Ar-*C*), 128.4 (Ar-*C*), 128.3 (Ar-*C*), 113.9 (4a-C), 99.6 (5-*C*H), 69.7 (O-*C*H_2-Ph), 32.3 (1'-*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (2 X CH_2), 29.5 (*C*H_2), 28.8 (*C*H_2), 27.6 (*C*H_2), 23.1 (*C*H_2), 14.6 (-CH_2CH_3).

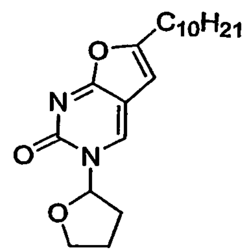
3-Benzyl-6-decyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2308



Also isolated from the crude residue was *the title compound* **53** (258 mg, 65 %) as white solid.

^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H, 4-H), 7.42 (m, 5H, Ar-C*H*), 6.07 (s, 1H, 5-H), 5.26 (s, 2H, N-CH_2-Ph), 2.67 (t, *J* = 7.3 Hz, 2H, 1'-CH_2), 1.83 (m, 2H, CH_2), 1.66 (m, 14H, CH_2), 0.93 (t, *J* = 6.9 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 172.3 (7a-C), 160.8 (2-C), 156.1 (6-C), 138.3 (4-*C*H), 135.9 (Ar-*C*), 129.6 (Ar-*C*), 129.1 (Ar-*C*), 129.0 (Ar-*C*), 108.6 (4a-C), 98.8 (5-*C*H), 54.4 (N-*C*H_2-Ph), 32.3 (1'-*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.4 (*C*H_2), 28.7 (*C*H_2), 27.2 (*C*H_2), 23.1 (*C*H_2), 14.5 (-CH_2CH_3).

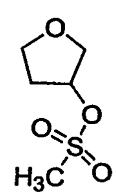
6-Decyl-3-(tetrahydro-furan-2'-yl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one Cf2249



26 (0.30 g, 0.19 mmol) and a catalytic amount of DMAP were suspended in dry DMF (8 mL) under an atmosphere of N_2, and 2-*tert*-butoxytetrahydrofuran **54** (0.34 mL, 0.31 g, 2.17 mmol, 2 equiv.) added *via* syringe with stirring. The resultant green suspension was heated to 150 °C for 5 h with stirring, then the solvent was removed under reduced pressure at 80 °C. The residue was purified *via* flash column chromatography in DCM to yield 90 mg (24 %) of *the title compound* **55** as a pale yellow compound.

^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H, 4-H), 6.10 (m, 2H, 5-H and 2'-H), 4.29 (m, 1H, 5'-H), 4.06 (m, 1H, 5'-H), 2.63 (t, 2H, *J* = 7.5 Hz, α-C*H*$_2$), 2.56 (m, 1H, THF-C*H*), 2.17 (m, 1H, THF-C*H*), 2.01 (m, 1H, THF-C*H*), 1.83 (m, 1H, THF-C*H*), 1.66 (m, 2H, C*H*$_2$), 1.30-1.1.9 (m, 14H, 7 x C*H*$_2$), 0.86 (t, 3H, *J* = 6.3 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 171.9 (7a-C), 160.0 (6-C), 155.2 (2-C), 134.2 (4-*C*H), 107.6 (4a-C), 99.1 (5-*C*H), 90.2 (2'-*C*H), 71.1 (5'-*C*H$_2$), 33.8 (*C*H$_2$), 32.3 (*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.7 (2 x *C*H$_2$), 29.5 (*C*H$_2$), 28.7 (*C*H$_2$), 27.2 (*C*H$_2$), 23.7 (*C*H$_2$), 23.1 (*C*H$_2$), 14.6 (*C*H$_3$).

Methanesulfonic acid tetrahydro-furan-3-yl ester 64

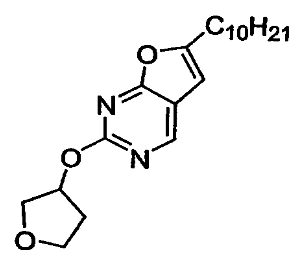


3-Hydroxytetrahydrofuran **57** (0.50 g, 0.46 mL, 5.5 mmol) and triethylamine (1 mL, 7 mmol, 1.3 equiv.) were dissolved in dry DCM (5 mL) and the solution cooled to 0 °C with stirring. Methanesulfonyl chloride **63** (0.55 mL, 7 mmol, 1.3 equiv.) was added slowly *via* syringe to the chilled solution. The solution was allowed to warm to RT, and the resultant suspension stirred at RT for 24 h. Dry DCM (20 mL) was then added to the suspension to

re-form a solution. The solution was allowed to stir at RT for a further 36 h. The solvent was removed *in vacuo* and the residue dissolved in water. The aqueous solution was extracted with DCM. The DCM extracts were then washed with brine, and the brine washings extracted with fresh DCM. The combined organic layers were then dried over $MgSO_4$. The solvent was removed under reduced pressure to yield **64** as a yellow viscous liquid (0.80 g, 96 %), which was used without further purification.

^{1}H NMR ($CDCl_3$) δ 5.20 (m, 1H, 1'-CH), 3.94-3.74 (m, 4H, THF-C*H*), 2.96 (s, 3H, C*H*$_3$), 2.18-2.11 (m, 2H, THF-C*H*); ^{13}C NMR ($CDCl_3$): 81.38 (1'-*C*H), 73.4 (2'-*C*H$_2$), 67.1 (4'-*C*H$_2$), 38.8 (*C*H$_3$), 33.7 (3'-*C*H$_2$).

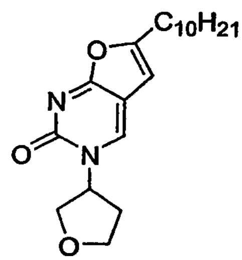
6-Decyl-2-(tetrahydro-furan-3-yloxy)-furo[2,3-*d*]pyrimidine 58



26 (0.182 g, 0.66 mmol), potassium carbonate (0.182 g, 1.33 mmol, 2 equiv) and methanesulfonic acid tetrahydro-furan-3-yl ester **64** (0.105 g, 0.63 mmol, 0.95 equiv) were suspended in dry DMF (5 mL) under N_2, and the reaction mixture heated to 80 °C with stirring for 8 h. The solvent was then removed *in vacuo* at 80 °C, and the resultant residue purified by flash chromatography in a 0-5 % methanol/DCM eluent gradient to yield **58** (140 mg, 62 %) as white solid.

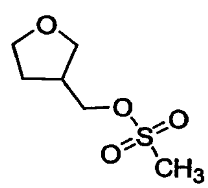
^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H, 4-H), 6.40 (s, 1H, 5-H), 5.64-5.59 (m, 1H, O-1'-THF), 4.07-3.96 (m, 4H, THF-C*H*), 2.80 (t, J = 7.5 Hz, 2H, 1'-C*H*$_2$), 1.79 (quin, J = 7.6 Hz, 2H, C*H*$_2$), 1.39-1.31 (m, 14H, C*H*$_2$), 0.93 (t, J = 6.5 Hz, 3H, -CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.6 (7a-C), 163.0 (2-C), 159.5 (6-C), 151.0 (4-*C*H), 114.6 (4a-C), 99.6 (5-*C*H), 78.2 (1'-THF-*C*), 78.2 (THF-*C*), 73.8 (THF-*C*), 67.7 (1'-THF-*C*), 33.5 (1'-*C*H$_2$), 32.3 (*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.5 (*C*H$_2$), 28.8 (*C*H$_2$), 27.6 (*C*H$_2$), 23.1 (*C*H$_2$), 14.6 (-CH$_2$*C*H$_3$).

6-Decyl-3-(tetrahydro-furan-3-yl)-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2276



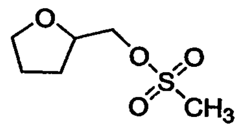
Also isolated from the residue was *the title compound* **59** as a white solid (22 mg, 10 %). ^{1}H NMR (CDCl$_3$) δ 8.00 (s, 1H, 4-H), 6.12 (s, 1H, 5-H), 5.68 (m, 1H, N-1'-THF), 4.23-4.09 (m, 2H, THF-C*H*), 3.97-3.86 (m, 2H, THF-C*H*), 2.68 (m, 2H, 1'-C*H*$_2$), 1.72 (m, 2H, C*H*$_2$), 1.36-1.30 (m, 16H, C*H*$_2$), 0.91 (t, J = 6.3 Hz, 3H, -CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 171.8 (7a-C), 160.7 (2-C), 156.0 (6-C), 136.0 (4-*C*H), 109.1 (4a-C), 99.1 (5-*C*H), 73.4 (1'-THF-*C*), 78.2 (THF-*C*), 67.6 (THF-*C*), 58.1 (1'-THF-*C*), 34.2 (1'-*C*H$_2$), 32.3 (*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.4 (*C*H$_2$), 28.7 (*C*H$_2$), 27.2 (*C*H$_2$), 23.1 (*C*H$_2$), 14.5 (-CH$_2$*C*H$_3$).

Methanesulfonic acid tetrahydro-furan-3-yl methyl ester 66



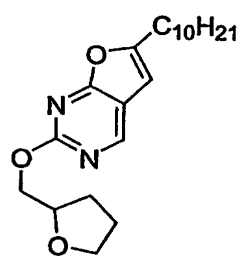
Tetrahydro-3-furan methanol **65** (0.50 g, 4.9 mmol) was dissolved in dry DCM (30 mL) and triethylamine (1.06 mL, 8.8 mmol, 1.8 equiv) was added to the solution *via* syringe under N$_2$ with stirring. The solution was cooled to 0 °C and methanesulfonyl chloride **63** (0.68 mL, 8.8 mmol, 1.8 equiv) added dropwise *via* syringe. The resultant solution was allowed to warm to RT and stirred at RT for 36 h. The solvent was then removed *in vacuo*. The residue was dissolved in fresh DCM and water (25 mL) added to the solution. The solution was then extracted with DCM. The DCM extracts were washed with brine, and the brine back-extracted with DCM. The combined DCM extracts were then reduced *in vacuo* to yield a yellow oil (**66**, 0.88 g, quantitative).

Methanesulfonic acid tetrahydro-furan-2-yl methyl ester 70



Tetrahydrofurfuryl alcohol **69** (0.50 g, 4.9 mmol) was dissolved in dry DCM (30 mL) and triethylamine (1.06 mL, 8.8 mmol, 1.8 equiv) was added to the solution *via* syringe under N_2 with stirring. The solution was cooled to 0 °C and methanesulfonyl chloride **63** (0.68 mL, 8.8 mmol, 1.8 equiv) added dropwise *via* syringe to the cooled solution. The resultant solution was allowed to warm to RT and stirred at RT for 36 h. The solvent was then removed *in vacuo*. The residue was dissolved in fresh DCM and water (25 mL) added to the solution. The solution was then extracted with DCM. The DCM extracts were washed with brine, and the brine back-extracted with DCM. The combined DCM extracts were dried ($MgSO_4$), then reduced *in vacuo* to yield a yellow oil (**70**, 0.86 g, 98 %).

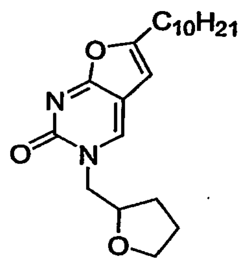
6-Decyl-2-(tetrahydro-furan-2-ylmethoxy)-furo[2,3-*d*]pyrimidine 71



26 (0.182 g, 1.086 mmol), potassium carbonate (0.182 g, 2.17 mmol, 2 equiv) and methanesulfonic acid tetrahydro-furan-2-ylmethyl ester **70** (0.186 g, 1.086 mmol) were suspended in dry DMF (5 mL) under N_2, and the reaction mixture heated to 100 °C with stirring under N_2 for 8 h. The solvent was removed *in vacuo*. The resultant residue was suspended in water (100 mL) and extracted with DCM (5 X 50 mL), then washed with brine. The combined DCM extracts were dried over $MgSO_4$, filtered, reduced *in vacuo* and purified by flash column chromatography in a carefully altered 0-5 % methanol/DCM solvent eluent gradient to yield 120 mg (32 %) of *the title compound* **71** as a white solid.

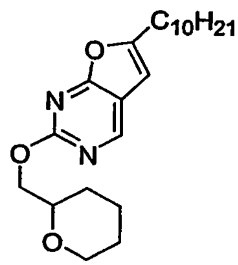
^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H, 4-H), 6.39 (s, 1H, 5-H), 4.49-4.36 (m, 3H, THF-C*H*), 4.03-3.94 (m, 1H, O-CH_2-THF), 3.91-3.84 (m, 1H, O-CH_2-THF), 2.79 (t, J = 7.4 Hz, 2H, 1'-CH_2), 2.19-1.84 (m, 4H, THF-C*H*), 1.80-1.73 (m, 2H, CH_2), 1.38-1.31 (m, 14H, CH_2), 0.93 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.6 (2-C), 159.3 (6-C), 150.9 (4-*C*H), 114.5 (4a-C), 99.5 (5-*C*H), 77.6 (THF-*C*), 70.1 (THF-*C*), 68.9 (O-1'-*C*H_2-THF), 32.3 (*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (2 X *C*H_2), 29.5 (*C*H_2), 28.8 (*C*H_2), 28.7 (*C*H_2), 27.6 (*C*H_2), 26.1 (*C*H_2), 23.1 (*C*H_2), 14.6 (-CH_2*C*H_3).

6-Decyl-3-(tetrahydro-furan-2-ylmethyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one 72



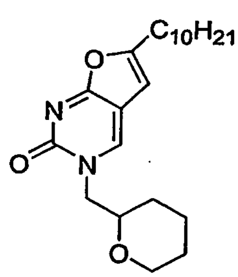
The title compound **72** (157 mg, 42 %) was also isolated from the reaction mixture as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H, 4-H), 6.13 (s, 1H, 5-H), 4.55 (dd, J = 2.3, 13.6 Hz, 1H, N-CH_2-THF), 4.29 (m, 1H, N-CH_2-THF), 3.93-3.72 (m, 3H, THF-C*H*), 2.68 (t, J = 7.4 Hz, 2H, 1'-CH_2), 2.26-2.15 (m, 1H, THF-C*H*), 2.00-1.90 (m, 2H, CH_2), 1.71-1.63 (m, 3H, THF-C*H*), 1.37-1.31 (m, 14H, CH_2), 0.93 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.4 (7a-C), 160.2 (2-C), 156.1 (6-C), 140.5 (4-*C*H), 107.9 (4a-C), 98.9 (5-*C*H), 77.3 (THF-*C*), 68.6 (THF-*C*), 54.9 (N-1'-*C*H_2-THF), 32.3 (*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.5 (*C*H_2), 29.2 (*C*H_2), 28.7 (*C*H_2), 27.2 (*C*H_2), 26.2 (*C*H_2), 23.1 (*C*H_2), 14.6 (-CH_2*C*H_3).

6-Decyl-2-(tetrahydro-pyran-2-ylmethoxy)-furo[2,3-*d*]pyrimidine 61



26 (0.30 g, 1.086 mmol), potassium carbonate (0.30 g, 2.17 mmol, 2 equiv) were suspended in dry DMF (5 mL) under N_2, and 2-(bromomethyl)tetrahydro-2*H*-pyran **74** (0.28 mL, 2.17 mmol, 2 equiv) added *via* syringe with stirring under N_2. The resultant mixture was heated to 110 °C with stirring overnight. The solvent was then removed *in vacuo* at 80 °C, and the residue suspended in water (100 mL) and extracted with DCM (5 X 50 mL). The combined DCM extracts were washed with brine, dried over $MgSO_4$, filtered, reduced *in vacuo* and purified slowly by flash chromatography in a DCM, then carefully altered 0-5 % methanol/DCM eluent gradient to yield *the title compound* **61** as a white solid (120 mg, 30 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H, 4-H), 6.38 (s, 1H, 5-H), 4.50-4.34 (m, 2H, O-C*H*$_2$-THP), 4.08 (m, 1H, THP-C*H*), 3.83 (m, 1H, THP-C*H*), 3.54 (t, *J* = 11.3 Hz, 1H, THP-C*H*), 2.79 (t, *J* = 7.4 Hz, 2H, 1'-C*H*$_2$), 1.97-1.94 (m, 1H, THP-C*H*), 1.76 (app d, *J* = 7.6 Hz, 2H, C*H*$_2$), 1.39-1.31 (m, 16H, C*H*$_2$), 0.93 (t, *J* = 6.5 Hz, 3H, -CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.6 (2-C), 159.3 (6-C), 150.9 (4-CH), 114.5 (4a-C), 99.5 (5-*C*H), 76.0 (THP-*C*), 71.3 (THP-*C*), 67.7 (1'-*C*H$_2$-THP), 32.3 (*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.5 (*C*H$_2$), 28.8 (*C*H$_2$), 28.5 (*C*H$_2$), 27.6 (*C*H$_2$), 26.3 (*C*H$_2$), 23.5 (*C*H$_2$), 23.1 (*C*H$_2$), 14.6 (-CH$_2$*C*H$_3$).

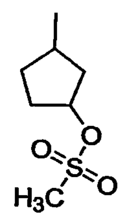
6-Decyl-3-(tetrahydro-pyran-2-ylmethyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one 62



Also isolated from the mixture was **62**, *the title compound* in 26 % yield (105 mg) as a white compound.

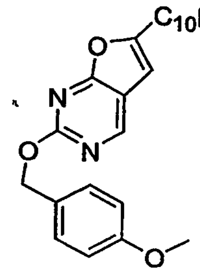
^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H, 4-H), 6.11 (s, 1H, 5-H), 4.48 (dd, J = 1.9, 6.7 Hz, 1H, N-CH_2-THP), 3.92 (app d, J = 10.7 Hz, 1H, THP-C*H*), 3.71 (m, 1H, THP-C*H*), 3.52 (app q, J = 4.5, 6.7 Hz, 1H, THP-C*H*), 3.38-3.30 (m, 1H, THP-C*H*), 2.66 (t, J = 7.4 Hz, 2H, 1'-CH_2), 1.97-1.94 (m, 1H, THP-C*H*), 1.88-1.47 (m, 4H, CH_2), 1.35-1.29 (m, 18H, CH_2), 0.91 (t, J = 6.5 Hz, 3H, -CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 172.5 (7a-C), 160.0 (2-C), 156.1 (6-C), 141.1 (4-*C*H), 107.5 (4a-C), 98.9 (5-*C*H), 75.3 (THP-*C*), 68.7 (THP-*C*), 56.6 (1'-CH_2-THP), 32.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 14.6 (-CH_2CH_3).

Methanesulfonic acid 3-methyl-cyclopentyl ester 76



3-Methylcyclopentanol **75** (0.5 g, 4.99 mmol) was dissolved in dry DCM (25 mL), and triethylamine (0.8 mL, 6.5 mmol, 1.3 equiv) added to the stirred solution under N_2, which was then cooled to 0 °C. Methanesulfonyl chloride (0.5 mL, 6.5 mmol, 1.3 equiv) was added dropwise *via* syringe to the chilled solution, the resultant solution warmed to RT and allowed to react at RT with stirring for 36 h. The solvent was removed *in vacuo*, and the residue dissolved in water (50 mL), which was extracted with DCM (5 X 50 mL). The combined DCM extracts were washed with brine (which was back extracted with fresh DCM (25mL)), dried ($MgSO_4$), filtered and reduced under vacuum to yield a clear yellow oil (789 mg, 88 %).

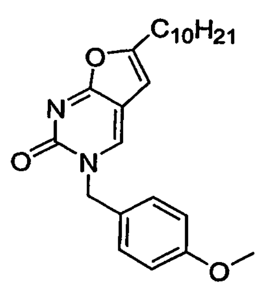
6-Decyl-2-(4-methoxybenzyloxy)-3*H*-furo[2,3-*d*]pyrimidine Cf2315



6-Decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one **26** (0.50 g, 1.81 mmol) and potassium carbonate (0.50 g, 3.62 mmol, 2 equiv.) were suspended in dry DMF (6 mL), and 4-methoxybenzyl chloride (0.5 mL, 3.62 mmol, 2 equiv) added to the stirred solution *via* syringe under N_2. The resultant mixture was heated with stirring to 120 °C overnight. The solvent were removed *in vacuo* at 80 °C, then the residue purified by flash column chromatography in a 0-5 % MeOH/DCM eluent gradient to yield *the title compound* X (63 mg, 9 %) as a white solid.

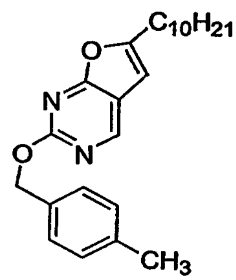
^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H, H-4), 7.48 (d, J = 8.4 Hz, 2H, Ar-C*H*), 6.93 (d, J = 8.7 Hz, 2H, Ar-C*H*), 6.35 (s, 1H, H-5), 5.44 (s, 2H, Ph-C*H*$_2$), 3.82 (s, 3H, O-C*H*$_3$), 2.77 (t, J = 7.3 Hz, 2H, α-C*H*$_2$), 1.75 (qt, J = 7.3 Hz, 2H, C*H*$_2$), 1.40-1.29 (m, 14H, C*H*$_2$), 0.91 (t, J = 7.0 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.2 (7a-C), 159.6 (C-2), 159.3 (C-6), 149.9 (4-*C*H), 130.8 (Ar-*C*H), 129.7 (Ar-*C*H), 116.2 (Ar-*C*H), 114.3 (Ar-*C*H), 99.7 (5-*C*H), 69.7 (Ph-*C*H$_2$), 32.3 (α-*C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 28.8 (*C*H$_2$), 27.6 (*C*H$_2$), 23.5 (*C*H$_2$), 21.1 (*C*H$_2$), 14.6 (*C*H$_3$).

6-Decyl-3-(4-methoxybenzyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2316



Also obtained from the mixture was the *title compound* as a white solid **34** (312 mg, 44 %). ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H, H-4), 7.35 (d, *J* = 8.0 Hz, 2H, Ar-C*H*), 6.95 (d, *J* = 7.8 Hz, 2H, Ar-C*H*), 6.06 (s, 1H, H-5), 5.18 (s, 2H, Ph-CH_2), 3.86 (s, 3H, O-CH_3), 2.66 (t, *J* = 7.5 Hz, 2H, α-CH_2), 1.69 (m, 2H, CH_2), 1.40-1.31 (m, 14H, CH_2), 0.93 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.4 (7a-C), 160.6 (C-2), 155.8 (C-6), 138.1 (4-CH), 130.7 (Ar-CH), 128.5 (Ar-CH), 114.9 (Ar-CH), 108.2 (4a-C), 98.9 (5-CH), 55.7 (O-CH_3), 54.0 (Ph-CH_2), 32.3 (α-CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 14.6 (CH_3).

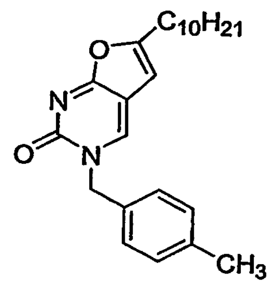
6-Decyl-2-(4-methylbenzyloxy)-3*H*-furo[2,3-*d*]pyrimidine Cf2313



6-Decyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one **26** (0.50 g, 1.81 mmol), potassium carbonate (0.50 g, 3.62 mmol, 2 equiv) were suspended in dry DMF (5 ml) and 4-methylbenzyl chloride (0.5 mL, 3.62 mmol, 2 equiv) added to the stirred suspension under N_2 *via* syringe. The resultant mixture was then heated at 100 °C overnight. The solvents were removed *in vacuo* at 80 °C and the resultant residue purified by flash column chromatography in a 0-5 % methanol/DCM eluent gradient to yield **30**, *the title product* (105 mg, 15 %), as a white solid.

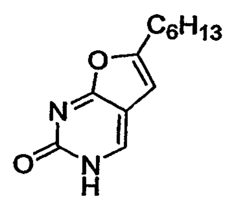
^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H, H-4), 7.45 (d, *J* = 7.9 Hz, 2H, Ar-C*H*), 7.21 (d, *J* = 8.0 Hz, 2H, Ar-C*H*), 6.40 (s, 1H, H-5), 5.49 (s, 2H, Ph-CH_2), 2.80 (t, *J* = 7.4 Hz, 2H, α-CH_2), 2.43 (s, 3H, Ar-CH_3), 1.79 (qt, *J* = 6.8 Hz, 2H, CH_2), 1.47-1.32 (m, 14H, CH_2), 0.94 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.2 (C-2), 159.3 (C-6), 149.9 (4-CH), 138.5 (Ar-CH), 129.5 (Ar-CH), 128.5 (Ar-CH), 114.3 (Ar-CH), 99.6 (5-CH), 69.6 (Ph-CH_2), 32.3 (α-CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 23.1 (CH_2), 21.7 (CH_2), 14.6 (CH_3).

6-Decyl-3-(4-methylbenzyl)-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2314



Also obtained from the mixture was the *title compound* **31** (440 mg, 65 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H, H-4), 7.30 (d, J = 8.2 Hz, 2H, Ar-C*H*), 7.23 (d, J = 8.0 Hz, 2H, Ar-C*H*), 6.05 (s, 1H, H-5), 5.20 (s, 2H, Ph-CH_2), 2.66 (t, J = 7.4 Hz, 2H, α-CH_2), 2.63 (s, 3H, Ar-CH_3), 1.73 (qt, J = 7.6 Hz, 2H, CH_2), 1.43-1.32 (m, 14H, CH_2), 0.92 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.3 (7a-C), 160.6 (C-2), 156.2 (C-6), 138.9 (4-*C*H), 132.8 (Ar-*C*H), 129.2 (Ar-*C*H), 128.5 (Ar-*C*H), 114.3 (Ar-*C*H), 98.8 (5-*C*H), 54.2 (Ph-*C*H_2), 32.3 (α-*C*H_2), 30.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.4 (*C*H_2), 28.7 (*C*H_2), 27.1 (*C*H_2), 23.1 (*C*H_2), 21.6 (*C*H_3), 14.6 (*C*H_3).

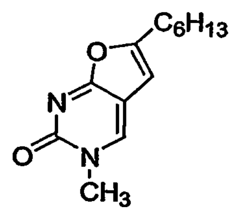
6-Hexyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



5-Iodouracil **23** (5.00 g, 21 mmol), tetrakis(triphenylphosphine)palladium(0) (1.0 g, 0.87 mmol, 0.04 equiv), and copper iodide (0.80 g, 4.2 mmol, 0.2 equiv) were dissolved in dry DMF (50 mL) with stirring under N_2. DIPEA (7.3 mL, 5.42 g, 42 mmol, 2 equiv), then 1-octyne (9.3 mL, 6.93 g, 63 mmol, 3 equiv) were added sequentially to the solution *via* syringe and the resultant solution, which darkened from golden to dark green over 20 min, left to stir at RT for 18 h. A further addition of copper iodide (0.80 g) was then made, followed by triethylamine (25 mL) and the resultant suspension heated at 120 °C for 6 h. The suspension was allowed to cool, the volume of solvent reduced to *ca.* 20 mL, and the solid collected by filtration, washed with DCM and methanol to yield a grey powder of

weight 3.13 g (38, 68 %). ^{1}H NMR ($CDCl_3$) δ 12.23 (br, 1H, NH), 8.16 (br, 1H, H-4), 6.38 (br, 1H, H-5), 2.65 (t, J = 7.1 Hz, 2H, α-C*H*$_2$), 1.63 (qt, J = 7.4 Hz, 2H, C*H*$_2$), 1.31 (m, 6H, C*H*$_2$), 0.88 (t, J = 6.4 Hz, 3H, C*H*$_3$).

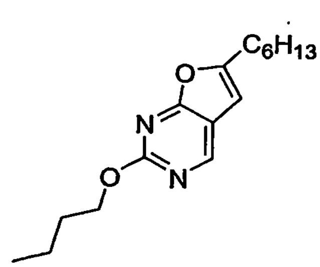
6-Hexyl-3-methyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2344



6-Hexyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one **38** (0.40 g, 1.82 mmol) and potassium carbonate (0.50 g, 3.64 mmol, 2 equiv) were suspended in dry DMF (5 mL) under N_2 and methyl iodide (0.23 mL, 3.64 mmol, 2 equiv) added *via* syringe to the stirred suspension, which was then heated to 80 °C overnight. The solvents were removed *in vacuo* and the crude purified by flash column chromatography in a 0-5% MeOH/DCM solvent gradient to yield *the title product* **40** as a white solid in very low yield (25 mg, 6 %).

^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H, H-4), 6.04 (s, 1H, H-5), 3.59 (s, 3H, N-C*H*$_3$), 2.59 (t, J = 7.5 Hz, 2H, α-C*H*$_2$), 1.63 (qt, J = 7.4 Hz, 2H, C*H*$_2$), 1.35-1.20 (m, 6H, C*H*$_2$), 0.83 (t, J = 7.0 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$), δ 172.5 (7a-C), 160.5 (C-2), 156.4 (C-6), 139.5 (4-CH), 108.3 (4a-C), 98.6 (5-CH), 40.2 (N-CH_3), 31.8 (α-CH_2), 29.1 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 14.5 (CH_3).

2-Butyloxy-6-hexyl-furo[2,3-*d*]pyrimidine Cf2346



6-Hexyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one **38** (0.40 g, 1.82 mmol), potassium carbonate (0.50 g, 3.65 mmol, 2 equiv) and 1-iodobutane (0.41 mL, 3.62 mmol, 2 equiv) were suspended in dry DMF (5 mL) under N_2 and heated to 80 °C with stirring overnight. The solvents were removed *in vacuo* and the crude purified by flash column chromatography in a 0-5% MeOH/DCM solvent gradient to yield *the title product* **42** as a white solid (180 mg, 36 %).

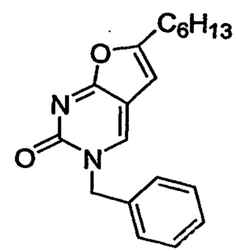
^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H, H-4), 6.34 (s, 1H, H-5), 4.42 (t, *J* = 6.6 Hz, 2H, O-C*H*$_2$-), 2.77 (t, *J* = 7.5 Hz, 2H, α-C*H*$_2$), 1.86 (qt, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.76 (qt, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.55 (m, 2H, C*H*$_2$), 1.43-1.31 (m, 6H, C*H*$_2$), 1.00 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 0.92 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.8 (C-2), 159.1 (C-6), 150.8 (4-CH), 99.6 (5-*C*H), 68.1 (O-CH$_2$-), 31.9 (α-*C*H$_2$), 31.3 (*C*H$_2$), 31.2 (*C*H$_2$), 29.1 (*C*H$_2$), 28.8 (CH$_2$), 27.6 (*C*H$_2$), 22.9 (*C*H$_2$), 19.6 (*C*H$_2$), 14.5 (*C*H$_3$), 14.2 (*C*H$_3$).

2-Benzyloxy-6-hexyl-furo[2,3-*d*]pyrimidine Cf2348

6-Hexyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (**44**, 0.40 g, 1.82 mmol) and potassium carbonate (0.50 g, 3.64 mmol, 2 equiv) were added under N_2 to dry DMF (5 mL), and the resultant suspension charged with benzyl chloride **43** (0.42 mL, 3.64 mmol, 2 equiv), then heated to 80 °C overnight. The solvents were removed *in vacuo* and the crude purified by flash column chromatography in a 0-5% MeOH/DCM eluent gradient to yield 39 mg (**44**, 7 %) of *the title compound* as a white solid.

^{1}H NMR ($CDCl_3$) δ 8.65 (br, 1H, H-4), 7.57 (d, *J* = 7.4 Hz, 2H, Ar-C*H*), 7.46-7.36 (m, 3H, Ar-C*H*), 6.38 (s, 1H, H-5), 5.53 (s, 2H, Ph-C*H*$_2$), 2.81 (t, *J* = 7.6 Hz, 2H, α-C*H*$_2$), 1.79 (qt, *J* = 7.4 Hz, 2H, C*H*$_2$), 1.47-1.33 (m, 6H, C*H*$_2$), 0.95 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.8 (7a-C), 162.5 (C-2), 159.4 (C-6), 150.9 (4-*C*H), 137.0 (Ar-*C*), 128.8 (Ar-*C*), 128.4 (Ar-*C*), 128.3 (Ar-*C*), 113.9 (4-*C*H), 99.6 (Ar-*C*), 69.7 (O-CH$_2$-Ph), 31.9 (α-CH$_2$), 29.1 (*C*H$_2$), 28.7 (*C*H$_2$), 27.1 (*C*H$_2$), 23.0 (*C*H$_2$), 14.5 (*C*H$_3$).

3-Benzyl- 6-hexyl-3*H*-furo[2,3-*d*]pyrimidin-2-one Cf2349



Also obtained from the purification process was *the title compound* **45** as a white solid (391 mg, 69 %).

^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1H, H-4), 7.49 (m, 5H, Ar-C*H*), 6.19 (s, 1H, H-5), 5.39 (s, 2H, Ph-C*H*$_2$), 2.76 (t, *J* = 7.4 Hz, 2H, α-C*H*$_2$), 1.80 (qt, *J* = 7.4 Hz, 2H, C*H*$_2$), 1.54-1.38 (m, 6H, C*H*$_2$), 1.02 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 172.2 (7a-C), 160.7 (C-2), 156.1 (C-6), 138.5 (Ar-*C*), 136.0 (Ar-*C*), 129.5 (2 x Ar-*C*), 129.0 (Ar-*C*), 128.9 (Ar-*C*), 108.6 (4-*C*H), 98.9 (5-*C*H), 54.5 (N-*C*H$_2$-Ph), 31.8 (α-*C*H$_2$), 29.1 (*C*H$_2$), 28.7 (*C*H$_2$), 27.1 (*C*H$_2$), 22.9 (*C*H$_2$), 14.5 (*C*H$_3$).

Biological Activity

Products where X=Y=N, Z=Q=O, U=V=CH and R^1, R^4 and R^8 are as given in Tables 1 and 2 below embodying the present invention were tested *in vtiro* in tissue cultures for toxicity and for potent antiviral actions with respect to cytomegalovirus (CMV). The results are given in Tables 1 and 2 below.

The column headings in Tables 1 and 2 are as follows:

R^1, R^4 and R^8 are as defined with respect to formula I above.

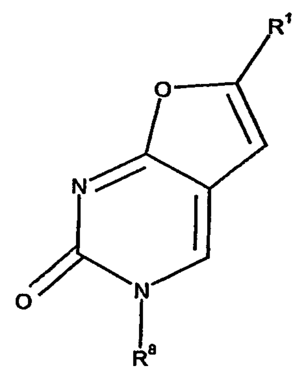
EC_{50}/μm CMV-AD169 is the drug concentration in μM required to reduce by 50% CMV strain AD169 induced cytopathicity in human embryonic lung fibroblast (HEL) cells measured 7 days post infection compared to untreated control.

$EC_{50}/\mu M$ CMV Davis is the drug concentration in µM required to reduce by 50% CMV strain Davis induced cytopathicity in human embryonic lung fibroblast (HEL) cells measured 7 days post infection compared to untreated control.

$CC_{50}/\mu M$ is the compound concentration required to reduce the cell number by 50%.

Further details of the methodology employed can be found in McGuigan *et al.* J. Med.Chem., 1999, 42, 4479-4484.

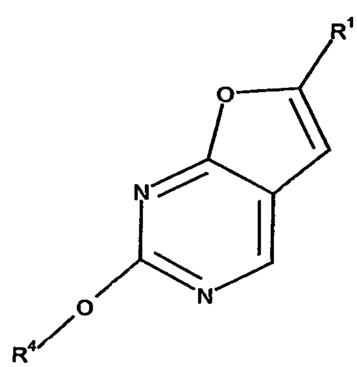
Table 1



No.	R^1	R^8	$EC_{50}/\mu M$ CMV AD169	$EC_{50}/\mu M$ CMV Davis	$CC_{50}/\mu M$
2158	nC_4H_9	Cyclo C_5H_9	>50	>50	ND
2160	nC_7H_{15}	Cyclo C_5H_9	5	4	194
2194	nC_4H_9	$CH(Et)_2$	>50	>200	>200
2190	nC_7H_{15}	$CH(Et)_2$	20	50	>200
2195	nC_4H_9	nC_5H_{11}	>50	>50	>200
2192	nC_7H_{15}	nC_5H_{11}	>200	>200	>200
2196	nC_7H_{15}	2-THF	>20	>20	46
2249	$nC_{10}H_{21}$	2-THF	>50	50	>200

2275	$nC_{10}H_{21}$	CH_2Cyclo C_6H_{11}	>200	>200	>200
2276	$nC_{10}H_{21}$	3-THF	20	10	148
2295	$nC_{10}H_{21}$	Cyclo C_6H_{11}	38	50	>200
2304	$nC_{10}H_{21}$	C_3H_7	40	8	>200
2306	$nC_{10}H_{21}$	nC_4H_9	>200	>200	>200
2308	$nC_{10}H_{21}$	$PhCH_2$	>40	>40	>200
2314	$nC_{10}H_{21}$	$TolCH_2$	>40	>40	>200
2316	$nC_{10}H_{21}$	$pMeOPhCH_2$	>200	>200	>200
2309	$nC_{10}H_{21}$	CH_2Cyclo C_5H_9	0.78	0.84	49
2344	nC_6H_{13}	Me	18	20	ND
2345	nC_6H_{13}	nC_3H_7	20	20	ND
2347	nC_6H_{13}	nC_4H_9	19	20	ND
2349	nC_6H_{13}	$PhCH_2$	>200	>200	ND

Table 2



			EC_{50}/µM		
No.	**R^1**	**R^4**	**CMV AD169**	**2 CMV Davis**	**CC_{50}/µM**
2159	nC_4H_9	Cyclo C_5H_9	8	7	108
2161	nC_7H_{15}	Cyclo C_5H_9	3	5	132

2193	nC_4H_9	$CH(Et)_2$	>20	>20	98
2189	nC_7H_{15}	$CH(Et)_2$	>5	12	98
2191	nC_7H_{15}	nC_5H_{11}	>5	16	1109
2247	$nC_{10}H_{21}$	nC_5H_{11}	>200	>200	>200
2250	$nC_{10}H_{21}$	Cyclo C_5H_9	>50	>50	>200
2252	$nC_{10}H_{21}$	$CH(Et)_2$	16	10	127
2294	$nC_{10}H_{21}$	Cyclo C_6H_{11}	12	16	>200
2303	$nC_{10}H_{21}$	nC_3H_7	2.5	2.1	126
2305	$nC_{10}H_{21}$	nC_4H_9	3.9	2.7	>200
2307	$nC_{10}H_{21}$	$PhCH_2$	3.3	1.1	>200
2274	$nC_{10}H_{21}$	$CH_2CycloC_6H_{11}$	4.4	2.9	>200
2313	$nC_{10}H_{21}$	$TolCH_2$	10.5	3.9	>200
2315	$nC_{10}H_{21}$	$pMeOPhCH_2$	3.3	2.9	>200
2343	nC_6H_{13}	Me	>8	4.7	ND
2346	nC_6H_{13}	nC_4H_9	8	3	ND
2348	nC_6H_{13}	$PhCH_2$	>200	>3.6	ND